CENTERS FOR DISEASE CONTROL BIRTH DEFECTS STUDY

HEARING

BEFORE THE

SUBCOMMITTEE ON
HOSPITALS AND HEALTH CARE

OF THE

COMMITTEE ON VETERANS' AFFAIRS
HOUSE OF REPRESENTATIVES

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CENTERS FOR DISEASE CONTROL BIRTH DEFECTS STUDY

WEDNESDAY, OCTOBER 3, 1984

House of Representatives,
Subcommittee on Hospitals and Health Care,
Committee on Veterans' Affairs,
Washington, DC.

The subcommittee met, pursuant to notice, at 10 a.m., in room 334, Cannon House Office Building, Hon. Bob Edgar (chairman of the subcommittee) presiding.

Present: Representatives Edgar, Kaptur, Penny, Rowland, Slattery, Daschle, Hammerschmidt, Solomon, Bilirakis, and Johnson.

Also present: Representative Don Edwards.

Mr. Edgar. The Subcommittee on Hospitals and Health Care will come to order.

Before reading my opening statement, I would like to make a personal statement. This is the last hearing that we will hold in this session of Congress, and I want to publicly state that John Paul Hammerschmidt, the ranking Republican on this subcommittee and on the full committee, has done an excellent job over the last 2 years, providing not only support but helping us to raise the right questions relating to health care.

So often we hold these hearings, and they are kind of pro forma discussions. We call each other gentleman and gentleperson and all of that type of thing, but I want to personally say to you, John Paul, that I have appreciated working with you over the past 2 years, specifically on this subcommittee.

And I want to congratulate you on what you have done to keep me on target, keep me pushed and really focused on the issues.

I want to also thank you for making this subcommittee as nonpartisan as it has been. We have our partisan differences from time to time, but I think particularly in the Veterans' Affairs Committee, we have done a good job of putting these aside, so I wanted to say to you, thank you for your help.

Mr. Hammerschmidt. Would the gentleman yield?

Mr. Edgar. I will yield briefly.

Mr. Hammerschmidt. I just want to respond by thanking you for those overly generous remarks, and also to commend you on your very vigorous and dedicated leadership.

You have done a fine job on this subcommittee. We all appreciate it. I know the veterans of the country appreciate it.

OPENING STATEMENT OF CHAIRMAN EDGAR

Mr. EDGAR. We are here today to receive testimony from the Centers for Disease Control, the Office of Technology Assessment, and the Science Panel of the Agent Orange Working Group on the report entitled, "Vietnam Veterans' Risks For Fathering Babies With Birth Defects."

Senator Alan Cranston, ranking minority member of the Senate Veterans' Affairs Committee, on August 17, asked that the Science Panel of the Agent Orange Working Group and the Office of Technology Assessment review the report and comment on the report with particular reference to the statistical power of the study.

He also requested an evaluation of three birth defects with statistically significant association to Vietnam service identified in the study.

These defects are spina bifida, a defective closure of the bony encasement of the spinal cord, through which the cord and meninges may or may not protrude; cleft lip with or without cleft palate; and other neoplasms which includes all the serious congenital tumors.

For many years, a number of Vietnam veterans have expressed concern that they may be of higher risk of fathering babies with certain birth defects.

I share their concerns, especially in light of the findings of the Centers for Disease Control birth defects study. The Office of Technology Assessment has reviewed the CDC study and has provided me with a copy of their review.

While I basically agree with their review, I still have questions concerning certain elements of the study, including the inexact determinant of agent orange exposure rates and their impact on the study results, as well as the absence of a rationale or explanation for the occurrence of birth defects in children of fathers exposed to agent orange.

I scheduled this hearing to, hopefully, receive some information on these very important findings and provide the Vietnam veterans with the plain facts concerning their risk of fathering children with birth defects.

I would now like to recognize the ranking minority member of the subcommittee, the Honorable John Paul Hammerschmidt of Arkansas, for any remarks he may wish to make. John Paul?

OPENING STATEMENT OF HON. JOHN PAUL HAMMERSCHMIDT, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ARKANSAS

Mr. HAMMERSCHMIDT. Thank you, Mr. Chairman.

The report of the Centers for Disease Control on birth defects in children of Vietnam veterans was reassuring, while still leaving some elements of concern for additional studies in the future. I have been impressed, Mr. Chairman, by the methodology of the Center, and by its candor when presenting reports.

It doesn't try to be absolute while scientific evidence is still sought. It has been my observation that it conducts itself in a classic scientific way, and I believe it deserves our commendation for not only the particular study, which is the subject of our hearing this morning, but for its many other studies.

It occurs to me, Mr. Chairman, that many of the matters with which the Congress must concern itself, such as agent orange and its effect, if any, on Vietnam veterans or their dependents, needs the highest degree of scientific and medical integrity.

I believe we are receiving it, and I congratulate the Centers for Disease Control for its fine efforts in research and for its searching for answers to very complex questions.

I am anxious to hear the testimony that will be offered this morning from these distinguished witnesses.

Mr. Chairman, I ask unanimous consent to place in the hearing record a copy of a letter I recently received from the Congressional Office of Technology Assessment, Dr. John Gibbons. His letter supports the statement that I just made.

Mr. **Edgar**. Without objection, that letter will be included.

[The information appears on p. 39.]

Mr. **Edgar**. Without objection, I would like to include in the record both the letter by Alan Cranston to the Agent Orange Working Group and their reply, which goes into some detail on the specific questions that Senator Cranston raises.

[The information appears on p. 57.]

Mr. **Edgar**. Also, before we hear from our first panelists, I might point out to the members here that we will have on the House floor today for the first time, an agreement between the House and Senate on agent orange, and atomic veterans compensation legislation.

Payment of compensation for two disabilities associated with agent orange, chloracne and prophyria cutanea tarda, a liver disorder, will be included in that legislation.

We also will have as part of that legislation for the first time a requirement that the Administrator issue regulations as to whether service connection shall be granted for thyroid cancer and two types of blood cancer which have been identified as statistically higher in atomic veterans—those veterans who have been exposed to atmospheric testing of nuclear weapons.

So it is an historic day today to deal with this study on birth defects, as well as the issue of compensation for exposure directly to agent orange and ionizing radiation.

I might just add one other personal note. My oldest son, who is now age 17½ and a freshman student at Temple University in Philadelphia, was born with a cleft palate and a hair lip. There is no more traumatic thing to happen to a young couple than to have their first son or daughter born with a birth defect, and birth defects do have not only the immediate impact, but also increase the long term pressures on those young couples.

So when we take up the issue of birth defects—while most of the news is good news, and I celebrate that—it is really important for us to ask tough questions and to analyze this study carefully because of the impact of birth defects throughout our society on the families of many people, some of whom believe that those birth defects may have been caused by exposure to some chemical or some action in Vietnam, and we will find out in more detail as we listen to our panelists.

Mr. **Solomon**. Mr. Chairman?

Mr. **Edgar**. I yield to my colleague.

Mr. SOLOMON. First of all, I want to concur in the remarks of both you and our ranking member, and apologize for having to leave this meeting. I am a conferee on the Export Control Act, and part of my subcommittee's legislation within that conference is coming up right now.

And I want to apologize for leaving, and again commend you and the ranking member and all other members of the committee, for the excellent work that they are doing on this subject.

I look forward to the results.

Mr. EDGAR. Dr. Rowland?

Dr. ROWLAND. No.

Mr. EDGAR. Our first panel consists of Dr. J. David Erickson of the Centers for Disease Control, who is accompanied by Dr. Peter Beach and Dr. Joseph Mulinare.

Dr. Beach will present the statement of Dr. Edward Brandt, Jr., Chairman pro tempore of the Cabinet Council Agent Orange Working Group.

Gentlemen, would you come forward at this point? Dr. Beach, are you going to make the initial presentation?

STATEMENTS OF PETER BEACH, EXECUTIVE SECRETARY, CABINET COUNCIL AGENT ORANGE WORKING GROUP; J. DAVID ERICKSON, PROJECT OFFICER, BIRTH DEFECTS STUDY, CENTERS FOR DISEASE CONTROL, DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND DR. JOSEPH MULINARE, MEDICAL EPIDEMIOLOGIST, CENTERS FOR DISEASE CONTROL

Dr. BEACH. Thank you, Mr. Chairman.

I have a very short statement to introduce myself, which I request be submitted to the record, then I will read in toto Dr. Brandt's statement to you.

Mr. Chairman, I am Dr. Peter Beach, Director of Veterans' Affairs for the Department of Health and Human Services, and additionally, the Executive Secretary and Staff Director of the Cabinet Council Agent Orange Working Group, part of the Cabinet Council on Human Resources of which Secretary Margaret Heckler is Chairman pro tempore.

I regret that the Chairman of the Agent Orange Working Group, Dr. Edward N. Brandt, Assistant Secretary for Health, is unable to present the following testimony due to a prior engagement, but would request that his testimony be included in the record.

With me today, on my right, is Dr. David Erickson who has a prepared statement and is the author of the CDC Birth Defects Study. With him is Dr. Mulinare also from CDC.

Now, if I may, I will summarize the following statement from Dr. Brandt. We will be available for questions following testimony.

Dr. Beach [reading]:

I am Dr. Edward N. Brandt Jr., the Assistant Secretary for Health and the Chairman Pro Tempore of the Cabinet Council Agent Orange Working Group. The Agent Orange Working Group coordinates and evaluates the comprehensive Federal research effort on the health effects, if any, of exposure to Agent Orange among Vietnam veterans.

I would like to clarify the role of the AOWG in the conduct of the Centers for Disease Control Study of Vietnam Veterans' Risks For Fathering Babies With Birth Defects.

As part of its mission, the AOWG has been intimately involved in reviewing and monitoring the progress of the CDC Birth Defects Study from beginning to end. This was accomplished primarily by two separate groups which report to me and to the Secretary of the Department of Health and Human Services, the Science Panel of the AOWG and the Advisory Committee on Special Studies Relating to the Possible Long-Term Effects of Phenoxy Herbicides and Contaminants, hereafter named the Advisory Committee.

The Advisory Committee, established according to the rules of the Advisory Committee Act, reports through me to Secretary Heckler both in her position as Secretary of DHHS and as chairperson pro tempore, Cabinet Council on Human Resources. The specific charters of the Advisory Committee and the Science Panel will be submitted for the record.

In the early stages of the CDC Birth Defects Study, the AOWG's Science Panel, which is composed of scientists from throughout the Federal Government, reviewed the proposed study for adequacy of design and recommended that the proposed study be performed.

In addition, an outside group of experts in birth defects and epidemiologic studies reviewed the protocol. When the study was completed this year, the Advisory Committee reviewed and analyzed the results before they were sent for publication in the Journal of the American Medical Association.

Members of the Advisory Committee are scientists who are drawn from outside the Federal Government. Outside membership assures the independence of an Advisory Committee review of a completed study.

The Advisory Committee may, at the discretion of the chair of the AOWG, undertake an evaluation and review of any ongoing study in the Agent Orange area at any stage of its progress.

This is the general procedure for an AOWG review of any study conducted by the Federal Government on the health effects of exposure to Agent Orange—namely, the review of the proposed study by the Science Panel and review of the completed study by the Advisory Committee.

This procedure was followed by the working group in its oversight of the CDC Birth Defects Study.

Since these reviews were so thoroughly performed, the unanimous view of the AOWG members at the September 20 meeting was that further review was unnecessary. During the discussion, it was pointed out that, in addition to the Science Panel and Advisory Committee reviews, reviews had been performed both internally by CDC and by independent reviewers for the Journal of the American Medical Association.

In all, reviews by five separate groups had been performed prior to publication of the Birth Defects Study.

In response to a Congressional request, the Science Panel has been directed to address the broader issue of whether more research on the question of a link between dioxin and birth defects is warranted. The AOWG believes this question to be both important and timely.

The Science Panel has recently formed a Subpanel on Research Agenda, and its first order of business will be to consider this question.

They met last week to do just that.

Since this research assessment will require appraisals of all published reports on this topic, we do not expect to be able to answer this question overnight. But we do plan to accomplish this task as quickly as possible.

In conclusion, it is the consensus of the AOWG members that the CDC Birth Defects Study is outstanding in both quality and scope. Through the Science Panel, the AOWG will undertake an assessment of whether there is a need for more research on the question of a relationship between Agent Orange exposure and birth defects in offspring.

We will convey to this committee the results of the deliberation of the Subpanel on Research Agenda as soon as the Agent Orange Working Group receives these results from its Science Panel.

I would be happy to entertain questions that you may have.

Mr. **Edgar**. Thank you.

We will hear from Dr. Erickson at this point. We appreciate your statement. We will save our questions until we have heard from the whole panel.

STATEMENT OF J. DAVID ERICKSON

Dr. **Erickson**. As you know, I am Dave Erickson from CDC Atlanta, and I am accompanied by Dr. Joe Mulinare. We are two of a very large team of investigators from CDC and other government agencies which participated in and made this study possible.

Mr. **Edgar**. Could I ask you to bring your microphone a little closer? That is much better.

Dr. **Erickson**. A summary of this study was presented in the August 17 issue of the Journal of the American Medical Association, and in the August 17 issue of the CDC's Morbidity and Mortality Weekly Report. A more comprehensive report of the study was also published by CDC.

Copies of these three reports have been made available to your subcommittee and I have additional copies with me if you wish them to be a part of the record.

Mr. **Edgar**. Without objection, we will make some of those a part of the file of the hearing, and make those that are reasonable part of the full hearing record.[1]

Dr. **Erickson**. This morning, I will briefly tell you about how CDC came to do this study, but most of my testimony will be about the study itself. In this testimony, I will quote liberally from the Morbidity and Mortality Weekly Report article.

In 1979, I was asked by the Director of CDC to serve on a Veterans' Administration Advisory Panel which had been formed to provide advice to the Administrator of Veterans' Affairs on matters related to Vietnam veterans' concerns about the possible health effects of exposure to herbicides.

As a member of the panel, I became aware of Vietnam veterans' specific concerns about their risks for fathering babies with birth defects. The potential for paternally derived birth defects as a result of chemical exposures is, however, largely unknown.

It is theoretically possible that such exposures in fathers could cause defects in three ways: One, by gene mutation; two, by chromosomal mutation; or, three, by acting as a fetal poison carried in the semen.

A potential for Agent Orange dioxin or causing defects by one or more of these mechanisms is unknown.

As I became aware of Vietnam veterans' concerns, I also realized that CDC was uniquely able to provide some answers to these concerns. This unique capability derived from CDC's Metropolitan Atlanta Congenital Defects Program, a program with which I was working at the time, and still am, a program which has registered babies born with birth defects since 1968.

In June 1979, I prepared a short internal memorandum which described the essence of the birth defects study which has just been completed.

CDC's capability became known to the White House-established interagency working group which had been charged with overseeing Federal efforts related to the health effects of herbicides.

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[1] The study summary published in the "Journal of American Medicine" appears on p. 127. The "Morbidity and Mortality Weekly Report" appears on p. 73. A copy of the "Vietnam Veterans' Risks for Fathering Babies with Birth Defects" published by the Centers for Disease Control is available for review in the Veterans' Affairs Committee of the House of Representations.

I presented the concept of this study to the group in the spring of 1980, and the group encouraged the development of a comprehensive study plan. A draft was completed in the summer of 1980.

This draft plan was given "human subjects" and peer scientific review by CDC staff employed outside of the operating component which would be responsible for conducting this study.

We invited four nongovernment scientists to come to Atlanta to provide further scientific review, and a scientific subcommittee of the interagency working group mentioned above reviewed the draft protocol.

Several veterans' service organizations were also invited to comment on the draft protocol. In the light of suggestions from these reviewers, the draft protocol was reviewed and submitted to OMB for final clearance to proceed.

In September 1980, CDC, the VA and the Department of Defense signed an interagency agreement to provide support for the study. In December 1981, a field test or pilot study was begun, and full-scale data collection began in May 1982 and was completed in the fall of 1983.

The data analysis and report writing took place at CDC during the winter and spring of 1984. The study reports were given very extensive peer scientific review at CDC and elsewhere.

The results were shared with the VA and DOD after the reports were in their final form and after the article which appeared in the Journal of the American Medical Association had been accepted for publication.

Let me now describe to you how the study was done and its conclusions.

Vietnam veterans' risks for fathering babies born with serious structural birth defects were assessed using a case control study. Case group babies, those with serious structural defects, were born during 1968 through 1980 and registered by CDC's Metropolitan Atlanta Congenital Defects Program.

This program, which I mentioned earlier, registers babies born with structural defects to women who are residents of the five-county metropolitan Atlanta area. To be included in the registry, a baby's defects must have been diagnosed during the first year of life and recorded on a hospital chart by a physician.

The use of this monitoring program as the source of cases for the study precluded analysis of other reproductive outcomes in the fathers, or functional deficits, such as mental retardation, in the babies.

Control group babies, those born without defects, were chosen from among almost 325,000 babies who were born in the same metropolitan area to resident mothers during the same period.

They were frequency-matched to the case group babies by race, year of birth, and hospital of birth. A total of 7,133 case group babies and 4,246 control group babies were eligible for the study.

In all, 4,929 mothers of case group babies and 3,029 mothers of control group babies completed interviews; fewer fathers completed interviews, about 3,900 from the case group, and about 2,400 from the control group. The major reason for parents' not participating in the study was that they could not be located after extensive searching.

Information about paternal military service in Vietnam was obtained through telephone interviews with the parents of the case and control group babies. Vietnam veteran fathers were asked if they believed they had been exposed to herbicides, such as agent orange.

In addition, a five-level "Exposure Opportunity Index", EOI, was defined based on activities that may have provided an opportunity for exposure to agent orange.

Vietnam veteran fathers were given subjective scores by the staff of the Army Agent Orange Task Force reflecting their presumed opportunities for exposure to agent orange.

The index scores were assigned on the basis of times and places of service in Vietnam and occupational duties while there. Scores were assigned without knowledge of the case/control status of the fathers.

Both parents were questioned about a wide variety of other potential risk factors for birth defects during the course of the interview.

In addition, Vietnam veteran fathers were asked whether they had contracted malaria in Vietnam and whether they had taken malaria chemoprophylaxis there.

The questioning of Vietnam veterans about malaria was done because malaria was a common disease among U.S. troops in Vietnam and because it was felt that veterans would be able to accurately relate an episode of the illness to an interviewer. We didn't ask these questions, because there had been some prior suggestion that malaria or malaria chemoprophylaxis in the father might cause birth defects.

Defects occuring among the case group babies were divided into 96 diagnostic categories for data analysis. Most of the 96 categories were composed of specific defects, such as anencephaly, a severe central nervous system defect; ventricular septal defect, a heart defect; and Down syndrome. Some categories were formed by grouping specific types of defects; one comprised all types of defects combined, that is, the complete case series.

For each of these 96 categories, four hypotheses were tested: One, whether veterans, including Vietnam veterans, were at different risk than nonveterans for fathering babies with birth defects; two, whether Vietnam veterans were at different risks for fathering babies with birth defects; three, whether Vietnam veterans who were judged by the Army Agent Orange Task Force to have had greater opportunities for exposure to agent orange had different risks for fathering babies with defects; and, four, whether Vietnam veterans who said during the interview that they had been exposed to herbicides, such as agent orange, were at different risks.

Testing the first hypothesis, determined whether, for the tests of the remaining three hypotheses, Vietnam veterans' risks should be compared with those of other veterans or with those of other veterans and nonveterans combined.

Testing the second hypothesis was the main focus of this study.

Fathers of 428 case group babies were Vietnam veterans; fathers of 268 control group babies were Vietnam veterans. Fathers of 4,387 case group babies and fathers of almost 2,700 control group babies were not Vietnam veterans.

The estimated relative risk of Vietnam veterans' fathering babies with defects when all types of defects are combined was 0.97, nearly 1.0. A relative risk of 1.0 would indicate that Vietnam veterans had the same risk of fathering babies with birth defects as other men; a relative risk which was less than 1.0 would indicate a lower risk and a relative risk of greater than 1.0 would indicate a greater risk for Vietnam veterans than the risk for other men.

With few exceptions, the estimated relative risks of Vietnam veterans' fathering babies with defects in the remaining 95 defect groups were similar to that found when all types of defects were combined.

Similarly, there was little evidence of different risks for Vietnam veterans who had been assigned higher agent orange exposure opportunity scores or for Vietnam veterans who had stated during the interview that they believed they had been exposed.

It was determined that, for most defect groups, Vietnam veterans' risks were neither higher nor lower than those of other fathers. In any large study in which multiple statistical tests are done, some exceptions are expected.

I am going to mention some of these studies' exceptions now.

First, the estimated risks for fathering babies with spina bifida—imperfectly formed spinal cord—were higher for Vietnam veteran fathers who received higher exposure opportunity scores.

Vietnam veterans who had higher scores had higher estimated risks for fathering babies with cleft lip with or without cleft palate.

Vietnam veterans who received higher scores had higher estimated risks for fathering babies with defects classified as "Other Neoplasms," which includes teratomas, neuroblastomas, and a variety of others. This category does not include certain neoplasms which are common at birth, such as hemangiomas, birth marks.

Vietnam veterans, in general, had a lower risk for fathering babies with cardiovascular defects classified as "complex" defects, two or more cardiovascular defects.

Vietnam veterans who stated they had contracted malaria while in Vietnam had a higher estimated risk for fathering babies born with hypospadias, a defect of the penis. No associations between risks of defects and use of malaria chemoprophylaxis were found.

The most important conclusion which I draw from this study is that the data collected contain no evidence to indicate that Vietnam veterans have had a greater risk than other men for fathering babies with defects when all types of serious structural birth defects are combined.

This study cannot exclude the possibility that some factor associated with service in Vietnam was or was not associated with the occurrence of rare types of defects, defects in the babies of selected individuals, or defects in the babies of small groups of veterans.

The conclusion, however, that Vietnam veterans in general have not fathered, at higher rates than other men, babies with defects when all types of birth defects are combined is based on pretty strong evidence.

All parents are at some risk of having a baby born with birth defects. Because this risk is always there, it is often called a "background risk." All men, whether Vietnam veterans or not, who father babies, have the same background risk, about two or three chances out of 100 that their babies will have serious structural birth defects.

It is useful to consider how this background risk has had an impact on Vietnam veterans. Suppose that each of the 2.6 million Vietnam veterans have had one baby each over the past 10 to 15 years. Then these men would have had 52,000 to 78,000 babies born with such problems.

If Vietnam veterans have had on average two babies each, then the figures mentioned above would be doubled.

Assessing Vietnam veterans' risks associated with exposure to agent orange is difficult. The measures of exposure that can be obtained today are imperfect, at best. The ability of Vietnam veterans to give valid reports of exposure is unknown, and the records used for the assignment of exposure opportunity index scores were made for military purposes, not for health studies.

This limitation makes it particularly difficult to assess whether the few statistically significant associations found in this study between defects and greater opportunity for exposure to Agent Orange, according to our index, are likely to reflect true effects of exposure or whether they are merely chance occurrences.

Moreover, the estimated relative risks for the exceptions presented here are rather low, in epidemiological terms.

These exceptions could conceivably be due to unmeasured confounding factors and may not be biologically significant.

The same reasoning can be applied to the statistically significant higher risk of hypospadias in babies whose fathers contracted malaria and the statistically significant lower risk of Vietnam veterans for fathering babies with complex cardiovascular defects.

That concludes my testimony. Dr. Mulinare and I will be pleased to answer any questions you might have.

Mr. **Edgar**. Dr. Mulinare, did you have any opening statement that you wanted to present?

Dr. **Mulinare**. No, sir.

Mr. **Edgar**. Let me yield to my colleagues first. I have a number of questions that I would like to ask, but I will give the first round of questions to my colleagues.

I yield to John Paul Hammerschmidt.

Mr. **Hammerschmidt**. Dr. Erickson, your study indicates that you determine that some veterans had "high exposure", to agent orange, while others had less exposure.

How exactly did you determine the amounts of exposure?

Dr. **Erickson**. Our study classified Vietnam veterans on what we call an exposure opportunity index, and underline the word "opportunity." We don't know today who was and who was not exposed to agent orange with any degree of certainty.

We don't know for sure what the opportunities may have been, but we tried, with the very fine help of Mr. Dick Christian, and the staff of the Army Agent Orange Task Force, to assign to each Vietnam veteran a score which we felt would reflect the opportunities of that veteran for having been exposed.

It is different than knowing exactly who was exposed and exactly how much, I must emphasize. The way that process was done was that, without knowing whether the Vietnam veteran in question had a baby with a defect, or whether the father had a control baby, a baby without a defect, information on the veteran's place of service in Vietnam, the time of service, his occupational duties, were integrated along with information taken from the records of the herbicide applications that exist in the military today.

And a subjective assessment was made, so basically we looked for proximity to applications of herbicides as determined from unit records, the time with respect to that proximity in space, and then the occupation of the individual, and we believe the occupation of the individual is an important aspect of this.

We believe that given a proximity in time and space to a particular application, that people with different occupations may have very different opportunities for having been exposed to agent orange.

Mr. EDGAR. If the gentleman would yield, I have a followup question.

Was there any determination between when a veteran was exposed, whether it high or low density, and the actual time of fathering the child?

Dr. ERICKSON. We did, in effect, two analyses which I didn't describe to you here this morning, which tried to get at that issue.

First, as a part of our overall analysis, we subdivided the case and control group babies into three time periods, three 52-month periods beginning in 1968, ending in 1980, to look to see whether there was any difference in Vietnam veterans' risk, depending on whether their babies were born in the early, middle or late seventies.

In effect, we didn't find anything very striking there, and that gives you some idea whether there is a time relationship, time of service in Vietnam, and most of our veterans were in Vietnam in the late sixties, and most babies were born in the early to late seventies.

We did an analysis in which time from discharge to time of birth of the baby was treated in a special and separate analysis, and again, we did not find anything particularly striking.

Thank you.

Mr. EDGAR. I yield back.

Mr. HAMMERSCHMIDT. Has your study been generally accepted in the scientific community, or have you received much feedback since it has been released?

Dr. ERICKSON. I think really, the only feedback that we have had, Mr. Hammerschmidt, is the feedback which we received from the groups which reviewed the studies prior to publication.

We received extensive feedback from the scientists , many, many scientists who reviewed the study, and I think had many, if not most, of the suggestions given to us incorporated into our final reports.

The reports were issued just over a month ago, and that is really not probably time for people to digest them and to give us feedback.

We would expect that if we are going to get feedback, it will come in the next few months.

Mr. HAMMERSCHMIDT. What was the cost of the study?

Dr. **Erickson**. We estimate that the cost exclusive of the cost of maintaining the registry over the years, specifically for this study the Federal Government spent roughly $2.8 million.

Mr. **Hammerschmidt**. That was paid for by appropriations to CDC?

Dr. **Erickson**. I am not just sure where the DOD and VA portions came from. CDC, which paid for more than a third of the study, paid for it out of its general pocket, there was no special appropriation.

Mr. **Hammerschmidt**. Well, I suppose that is sort of irrelevant to our questioning here this morning, but we sometimes hear that the VA or for that matter, other agencies in a similar situation cannot fairly study such a matter as this.

Without accepting that conclusion as being valid, tell us which, if any, of the agencies were interested in your work, Doctor.

Dr. **Erickson**. We received much interest and very good cooperation from the project officers, Dr. Barclay Shepard at the VA, and Dr. Jerry Bricker at DOD.

Who were the people we had contact with? I mentioned the fine work of the Army Agent Orange Task Force; which the expense of that work was not included in the $2.8 million, nor in the money contributed for the study under an interagency agreement by the DOD.

Mr. **Hammerschmidt**. Thank you, Dr. Erickson.

Mr. **Edgar**. I would like to yield to my colleague, Don Edwards. Don and I sent a letter in 1978 on the issue of agent orange to try to get this committee to begin to hold some hearings on the issue, and he has been a leader in trying to help people understand the impact of exposure to systemic problems.

I will yield to him at this time.

Mr. **Edwards**. Thank you, Mr. Chairman. We continue the work of the subcommittee in this important area.

Dr. Erickson, to follow what Mr. Hammerschmidt was asking you, did you submit a draft of the report to the DOD, OMB, the VA or the Army Agent Orange Task Force for comments before it was printed?

Dr. **Erickson**. No, sir, with one exception. The VA did not see the draft of the study report, nor did the DOD people see any draft study report, except that a section of the report which dealt with the methods of the agent orange exposure opportunities, not the results, but the methods of the agent orange opportunities index in our comprehensive report, were reviewed by the Army Agent Orange Task Force for accuracy prior to publication.

Mr. **Edwards**. Did they make any suggestions?

Dr. **Erickson**. I am going to have to defer to Dr. Mulinare to answer that question.

Dr. **Mulinare**. I believe there were suggestions made with regard to the vocabulary that we used. My lack of experience in the use of Army records and the special efforts that they had to use to go into them required editing on their part with regard to the vocabulary.

Mr. **Edwards**. Is the report essentially the same, after it had been reviewed by the task force?

Dr. **Mulinare**. I believe so.

Mr. **Edwards**. In what way was it changed?

Dr. **Mulinare**. I am sorry. I don't think it was changed.

Mr. **Edwards**. You believe it was the same. Was it changed in any way?

Dr. **Mulinare**. Except for the vocabulary changes and perhaps in some of the areas, specifically defining certain aspects of the records that we used, no.

Mr. **Edwards**. Lastly, Mr. Chairman, this report was circulated to scientists and doctors throughout the United States. I believe you so testified, Dr. Erickson? Did you circulate the report to the 50 or 100 scientists and doctors who were in Vietnam, and I believe in 1981 or 1982 for the study that was made there?

Dr. **Erickson**. Not to my knowledge. Maybe I can explain the review process to you.

I will explain it in a little more detail. Our report, written by the study team in its first draft form, was reviewed by a group of CDC employees who work in the Center for Environmental Health.

Our birth defects program, from which Dr. Mulinare and I come, is situated in the Center for Environmental Health. Once we incorporated suggestions made by those reviewers, the Centers for Disease Control Director established a panel of scientists in CDC, outside the Center for Environmental Health.

They reviewed the document, made suggestions, and we responded to those suggestions.

Then, the report was sent to the Journal of the American Medical Association for consideration for publication. As a part of their consideration process, they submitted the draft report, the draft summary report and the comprehensive report to, I believe, seven reviewers, seven reviewers who are unknown to us, and it is possible that one or more of those reviewers was among this group.

Last, the Science Panel of academic scientists which reports to the Agent Orange Working Group, also reviewed these documents.

To my knowledge, none of the members of that panel were in this group who went to Vietnam.

Mr. **Edwards**. Thank you, Mr. Chairman.

Mr. **Edgar**. Before I yield to Mr. Bilirakis, are there other studies concerning dioxin exposure birth defects, either ongoing or planned, of which you are aware externally from this particular study of the veterans?

Dr. **Erickson**. Dioxin or agent orange?

Mr. **Edgar**. Let me ask first about dioxin and if there are any private sector studies being done in the area of agent orange exposure?

Dr. **Erickson**. The only study of which I am aware which specifically speaks to dioxin is the National Institute for Occupational Safety and Health Dioxin Registry, which concerns workers who have been exposed to dioxin in industrial accidents.

Mr. **Edgar**. Has there been a birth defect analysis of those workers?

Dr. **Erickson**. Not yet, and I think the protocol for the morbidity phase of that particular study which may or may not include a look at birth defects is under review by the Science Panel of the Agent Orange Working Group.

Mr. EDGAR. Dr. Beach, do you have anything to add to that in terms of studies that might be available in the areas of dioxin or agent orange as it relates to birth defects that are ongoing or have been completed?

Dr. BEACH. Mr. Chairman, only as referred to in the full reply that you have entered into the record, that is to say the letter to Senator Cranston from Dr. Brandt which specifically mentioned the proposed studies of dioxin exposure and the production of birth defects that NIOSH will be addressing, and the broader issues of morbidity among workers at two industrial plants. There will be a very extensive review of these proposed studies and the draft protocols will be referred to the Science Panel for review and they will be the subject of response to you and this committee.

Mr. EDGAR. Thank you. We will focus on that as the studies proceed. Let me yield to Mr. Bilirakis.

Mr. BILIRAKIS. Thank you, Mr. Chairman.

Dr. Beach, you are listed here as the executive secretary, Cabinet Council, AOWG.

Who do you work for?

Dr. BEACH. Congressman, I am a career Federal employee working for the Department of Health and Human Services where I am the Director of Veterans' Affairs. My primary job is the Director of Veterans' Affairs.

I do, however, work on the Cabinet Council as the Executive Secretary, Staff Director, which is my other hat.

Mr. BILIRAKIS. Sir, are you a medical doctor?

Dr. BEACH. No, sir.

Mr. BILIRAKIS. You are not. I would ask Dr. Erickson and Dr. Beach now, as Ph.D.s, as members of the medical community for many, many years, was this a good study? If you were not members, or were not employees of the Federal Government, if you were a layman Ph.D. or a layman member of the medical community, would you consider this to be a good study?

Dr. ERICKSON. I am not sure I can give you an unbiased view, but yes, I am proud of the job we did.

Dr. BEACH. That is the consensus, Congressman, of the Cabinet Council Agent Orange Working Group.

Mr. BILIRAKIS. I know many questions were asked about cooperation with DOD and other agencies and other groups. Are there any ways in which you, if you had your druthers and had it to do over again, that you maybe would change this study?

I don't know that I am talking about unlimited financial resources there. Well, would you say that the study was conducted as well as could be expected?

Dr. ERICKSON. Well, I think, given our starting point, which was the Metropolitan Atlanta Congenital Defects Program Registry, I don't know that we would do it very much differently.

Very little that I can think of.

Mr. EDGAR. Would the gentleman yield?

Mr. BILIRAKIS. Sure.

Mr. EDGAR. It is real tough for you to answer a question about what you would do differently, but let me ask you specifically, in relation to Mr. Bilirakis' question. If you had access to 172 hospitals across the country where Vietnam veterans were seeking medical care, what kinds of questions might you want asked by the medical staff, so that 5 years from now, or 10 years from now, when we revisit this issue, we would have substantive material for you to study?

Are there those such questions that you would want veterans who are getting into that health care system to be asked in their history-taking that could be helpful to future studies?

Dr. ERICKSON. Relative to reproductive problems?

Mr. EDGAR. That is correct.

Dr. ERICKSON. No, I would think not. That would not be the best way to approach that.

Mr. EDGAR. Thank you.

Mr. BILIRAKIS. You would say, then, that having limited the study to the Atlanta metropolitan area that that area could be considered representative basically of other parts of the country?

Dr. ERICKSON. We don't have any knowledge which would suggest otherwise. It is also possible. As I said earlier, in my statement, CDC was almost uniquely able to do this study because of the existence of that registry.

That registry is, I think I can say without too much hubris that it is a unique national resource, and made it possible for us to do this study quickly, at least in terms of doing epidemiological studies.

Mr. BILIRAKIS. Would the fact that the registry is limited to birth defects discovered or diagnosed during the first year of life, is that valid?

I suppose it is conceivable that there may have been defects which may not have been diagnosed until after the first year. Would many instances of that have occurred?

Dr. ERICKSON. No, there are certain kinds of defects which are diagnosed sometimes after the first year of life. Most of the serious structural defects, though, are diagnosed during the first year of life.

Problems which we were unable to deal with would include things such as mental retardation unaccompanied by structural, physical malformations.

That is not part of our study and we have no evidence one way or another regarding them, nor is there any registry which would allow us to do the study that I am aware of.

Mr. BILIRAKIS. Just one last question, Mr. Chairman. I am concerned with the veracity of the study, the overall veracity of it. In 1979 you were asked by the Director of the CDC to serve on a VA Advisory Panel to provide advice to the then-Administrator of Veterans' Affairs.

In June of 1979, you prepared a short internal memorandum, and this is a scenario describing the essence of the first defect study, which has just been completed.

In other words, at that time, you prepared a short internal memorandum regarding a study that had taken place up to that point?

Dr. ERICKSON. A short internal memorandum which described the essence of the plan for the study which we have just completed.

Mr. BILIRAKIS. Then you printed the concept of that plan, to the group in the spring of 1980 and the group then encouraged the development of a comprehensive study plan and a draft was completed in the summer of 1980, and then the draft was given "human subjects," I don't quite understand, but does that form mean "laymen"?

Dr. **Erickson**. That is jargon, basically, in our institution and any other Federal or academic institutions in the United States, any time there is research done involving human subjects, the research plan must undergo a review by a panel for them to ensure that the plan is ethical, and that there are no abuses of the people who might participate in the study.

Mr. **Bilirakis**. Thank you for that explanation.

Going on, peer scientific review by CDC staff was employed outside of the operating component which is significant, and then you went on, and invited four nongovernmental scientists to come to Atlanta to provide further scientific review, and you mentioned several veterans' organizations were also invited to comment on the draft protocol. Is it true that all of these people were asked for input regarding the plan for the study?

Dr. **Erickson**. Yes, sir.

Mr. **Bilirakis**. All right, so now, the study has been completed. We have had publication in the American Medical Journal, and we have a copy of that here.

Have any peer groups, human subjects, veterans' organizations, et cetera, been invited to comment on the final results of the study?

Dr. **Erickson**. I think the latest count is, outside of CDC, 22 individual scientists participated in the review of the reports prior to publication.

Prior to the release of the reports publicly, I personally briefed representatives from the veterans' service organizations here in Washington, and that briefing was done after the reports had been accepted for publication, but prior to their release, and I have received no personal correspondence from those people, although we were given to feel that they felt at that briefing that we had done a reasonable job for them.

Mr. **Bilirakis**. OK, so we—we meaning the Veterans' Administration, CDC, Members of Congress, officially have not received any response or any reaction from the veterans' organizations at this point regarding the study. Is that correct, would you say, Mr. Chairman?

Mr. **Edgar**. It has only been out a month, and we have begun to receive some responses from a number of people who are looking at it, raising some questions which I will be asking in terms of pieces of the protocol, but I don't think we have had any definitive response from the service organizations.

Mr. **Bilirakis**. I assume we will.

Mr. **Edgar**. Two days before adjournment, I chose not to get official statements from the service organizations only because of the time and space, but we look forward to their analysis.

Mr. **Bilirakis**. Thank you, Mr. Chairman. Thank you, gentlemen.

Mr. **Edgar**. Dr. Rowland?

Dr. **Rowland**. You say the estimated risks for fathering babies with spina bifida were greater for those veterans who had higher exposure opportunity scores?

What do you mean by estimated risk?

Dr. **Erickson**. This is a complicated statistical issue.

Two things we mean by estimated, first, we have a sample here. We do not have the whole population. Any time you are dealing with a sample, you are trying to estimate some underlying measure like risk in a population, so it is an estimate, in that sense.

Second, we use a statistical measure called an odds ratio, which is an approximation of a relative risk—relative risk, the idea of the the Vietnam veterans having a baby with spina bifida relative to the risk for men who are not Vietnam veterans.

This odds ratio is an estimate of it.

Dr. **Rowland**. Would that not here be comparable to a double blind study?

Dr. **Erickson**. No; I would say not. Much of our information was gathered by interviewers who were blind to the case control status of parents, but the parents themselves could not be blind, the fact of their baby being normal or not normal, and so on.

Dr. **Rowland**. In the assessment of those that may have had spina bifida, was any consideration given to what sort of damage may have been incurred in the peripheral nervous system?

Dr. **Erickson**. I missed one word out of your question.

Dr. **Rowland**. Damage to the peripheral nervous system in spina bifida, were there any estimates of what might have been a variation in that damage?

Dr. **Erickson**. No.

Dr. **Rowland**. All right. We are also talking about defects that were manifest at the time of birth, or would have appeared at the time after birth. Was a year mentioned?

Dr. **Erickson**. Yes.

Dr. **Rowland**. Defects that might not become manifest until after a year? Would you elaborate just a little bit on that, and you did not assess those types of defects in this study?

Dr. **Erickson**. Well, yes and no. We did not assess defects which were recognized in a particular child after 1 year of age, but those defects which are not recognized until later in life tend to be things such as internal malformations, some types of heart malformation, for example.

Most of those are recognized prior to the first year of age and we did make an assessment, for example, of ventricular septal defect which is sometimes not recognized until later in life, but we had many babies with ventricular septal defect in our study because their defects were diagnosed in their first year.

Dr. **Rowland**. Since we are trying to assess what type of problem dioxin might cause in relationship to congenital defects, could we say that the study is incomplete in that respect?

Dr. **Erickson**. You would have to call it incomplete in that sense, in a strict sense you would, although I think that there would be relatively few more babies added to our study if we had followed the diagnoses into later life. I think the incompleteness with respect to reproductive outcomes is more along the lines that we were not able to study such problems as mental retardation or functional deficits.

Dr. **Rowland**. You mentioned that in talking with Mr. Bilirakis a few minutes ago, and I just have the feeling that while this is very helpful, there is still something left that has not been assessed.

Thank you very much.

Mr. **Bilirakis**. Mr. Chairman, may I hitchhike for a moment?

Dr. Rowland, are you basically saying you feel possibly the registry should have been expanded maybe to an additional period of time over and above the first year?

Dr. **Rowland**. It would take a long time, I think, in order to determine what the effects will be eventually, and yes, I do believe that.

Mr. **Edgar**. I yield to Mr. Daschle.

I have a series of questions I do want to specifically ask relating to some of the issues that have been raised here.

Mr. Daschle?

Mr. **Daschle**. I would like to pursue a statement that will be made a little later on this morning, regarding the Office of Technology Assessment.

This statement relates to the exposure opportunity indices that you mentioned in your testimony. OTA in their testimony before us this morning states that the exposure opportunity indices may not provide an approximation of relative exposure to agent orange.

They go on to say that the indices represent service in combat units at least as much as they do, exposure to agent orange, and because combat plays such an important role in exposure ratings, and the true relative exposure ratings may be entirely obscured.

If this is the case, and we believe it very possibly is, associations with the indices would have no meaning. What makes this such a vexing problem is that there does not exist, nor is there in prospect a way to validate any exposure index such as the ones used in this study.

This is quite a statement, and I am going to be very interested in pursuing this with them, but if that is the case, it has a real ramification with regard to the evidence that you have suggested this morning in your testimony.

How would you respond to this criticism?

Dr. **Erickson**. Well, first, I would like to make very clear, Mr. Daschle, that—we have said repeatedly in our reports and so on—that the accuracy of these indices are unknown as to reflecting true exposure to agent orange.

We think, however, they are as good as could be practically done, and I think that we could have some disagreement with the people from OTA on specific issues. I think it boils down to whether occupation is factored into an assessment of the exposure possibilities for an individual veteran.

We believe that it should.

Mr. **Daschle**. I am concerned that we really have no way of judging the indices, I would assume that you would have no way of judging real exposure and if you have no way of judging real exposure, it would be difficult to judge what effects a prospective exposure would have.

Dr. **Erickson**. Yes, and I think in our reports we do state that these are imperfect at best, and that we wanted to do something, we wanted to do as good a job as we could in trying to get at some measure of possible exposure.

I think that we state that we feel we have strong evidence to support our statements that Vietnam veterans in general have not been at an increased risk. We also state that whatever conclusions we make about the associations with the agent orange exposure opportunity index are based on considerably weaker evidence.

Mr. **Edgar**. Would the gentleman yield at that point?

If I could just clarify, I think that the gentleman is asking a good question here. As I understand your study, let me see if I can be as simple and specific as possible, there is not any significant example of birth defects being caused by exposure overall, in terms of the study of Vietnam experience.

And second, when the participants are asked were you, or were you not exposed, there does not seem to be any overall indices of birth defects, but when you compare that to the military's analysis of who in fact was exposed to agent orange, that is where you get the blip in the three areas of the indices, is that correct?

Dr. **Erickson**. With one slight modification, the military's assessment of who had opportunities for exposure.

Mr. **Edgar**. Military analysis of who had exposure to agent orange, that is where you find the spina bifida, cleft palate and the other disorders that you related?

Dr. **Erickson**. Correct.

Mr. **Edgar**. That is very important to lay out that as A, B, C, and A and B being no significant difference, and C, being where there was significant difference.

Dr. **Erickson**. One significant difference for Vietnam veterans overall, not an increase, a decreased significant difference for these complex cardiovascular defects.

Mr. **Daschle**. You seem to be saying that you are more confident of your findings than you are of your indices. Am I to understand you right?

Dr. **Erickson**. We are quite confident of our findings for Vietnam veterans' risks, overall, regardless of exposure possibilities.

With regard to our findings in association with exposure possibilities, we are much less certain, and those uncertainties derive from our uncertainties about the validity of the index of exposure.

Mr. **Daschle**. I am not a doctor, but it seems incongruous to me that you could be doubtful about your indices and about the exposure, but draw some firm conclusions from the fact that you have studied these people regardless of what exposure they may have had and be more confident with those findings.

As the chairman said, within certain categories, I suppose, those findings can be more appropriately determined, is that correct?

Dr. **Erickson**. Well, overall, it is a big problem. Two or 3 percent of babies are born with serious defects; and it is possible that Vietnam veterans have no increased risk overall that we can detect, but yet, still be an increased or decreased risk for some subset of the 2 or 3 percent, for some rare kind of defect or maybe there is some particular subset of Vietnam veterans who are at increased risk that our study is not able to demonstrate with a degree of certainty.

Mr. **Daschle**. Do you agree or disagree with the statement, OTA summarizes their comments by saying, if the indices are invalid, however, the agent orange analysis provided—I am sorry—the agent orange analysis provides no reliable information either to rule out association with agent orange or to confirm them.

Would you agree with that?

Dr. ERICKSON. If the indices are invalid, and if they have no correlation with true exposure, which we don't know, but if they do not, they have no particular ability to rule in or rule out, I would agree.

The question is whether these indices do have some correlation with true exposure or whether they don't. We have no way of knowing that, no way for us to measure that today.

We think that the way the exposure indices were constructed makes sense, and that is about as much as we can say.

Mr. DASCHLE. You apparently do agree about the indices, and you then also agree you cannot either rule our association with agent orange or confirm them?

Dr. ERICKSON. If the index is not in any way correlated with true agent orange exposure, if that is the case.

Mr. DASCHLE. Do you think that is the case?

Dr. ERICKSON. I don't know. It makes sense to me that it ought to give this some approximation of exposure possibilities. Some rough approximation, I don't know how rough it is.

Mr. DASCHLE. OK. That, again, seems to me to undermine the confidence that one would have in the findings themselves.

Let me ask one other question and this is related, in dealing with the index findings that you discussed, you found that there were significantly higher numbers of children with birth defects who were born in the non-Vietnam veterans' group, the relative risk of the index child being 2.57.

If we look beyond the second child, Vietnam veterans, according to your study, appear to be at a greater risk than the control group. Is that an accurate assessment of your findings?

Dr. ERICKSON. I am not sure I understand your question.

Mr. DASCHLE. You found after the index baby, significantly higher numbers of children with birth defects were born in the non-Vietnam veterans' group, the relative risk after the index child being 2.57. How do I interpret that?

Do I understand that to mean in the Vietnam veterans' group that 2.57 would indicate that there is a higher risk of birth defects in the index baby than in the control group?

Dr. ERICKSON. That particular figure derives from our assessment of whether Vietnam veterans had increased risk of having more than one baby, not necessarily after the index baby, but more than one baby, two or more babies with birth defects.

We did find some indication that that might be so.

Mr. DASCHLE. There was a greater indication that they would have more than one baby with birth defects?

Dr. ERICKSON. Yes.

Mr. DASCHLE. Thank you, Mr. Chairman.

Mr. EDGAR. Dr. Erickson, what surprised you about the study?

Dr. ERICKSON. I think what surprised me about the study was the difficulty in getting it done. It was very, very difficult to locate people. And that took us a lot more time than I had expected and some more money.

Mr. EDGAR. Follow up with the surprise question. I am interested in after you did all of the findings, and you made your analysis, if you were going to speak to a Rotary Club or Lion's Club or a group with the medical background that you have, and you were going to explain the findings of your study, both in terms of its overall finding, secondarily, the few blips that you did find, how would you express that to that group?

Dr. ERICKSON. Well, I think that I would say that so far as the evidence we have at hand, Vietnam veterans do not have an increased risk at having babies with birth defects, and if we were in a situation of counseling prospective parents, we would not counsel them any differently than those who did not serve in Vietnam.

We would counsel them about things which make for a healthy pregnancy, healthy baby, rubella immunization, not smoking, not drinking too much, things of that sort, but we wouldn't worry particularly about the fact of a prospective father being a Vietnam veteran.

Mr. EDGAR. Could you assure the veterans' population, particular of Vietnam, that they are, to your study, there was no gene mutation?

Dr. ERICKSON. Assure, no, sir. Our study does not assure anything like that, although I may say, Mr. Edgar, that we did make a special analysis of the group of babies with defects which were thought to be caused by new gene mutations.

It is a small group of babies, but there were no Vietnam veteran fathers among the fathers of those babies.

Mr. EDGAR. I am a father of a baby that was born with a cleft palate and hair lip, and you indicate that there is an increase in that area.

Can you describe, first, how significant the finding was in terms of cleft palates—excuse me—hair lips? If you are saying that spina bifida and cleft lips were a significant difference, I would like you to be clear with us as to how big—big significance, little significance?

Dr. ERICKSON. I think that in terms of what we deal with as epidemiologists and what the tools of our trade allow us to do, that the increases in risks that we have estimated for our study are rather small.

It may not seem so to somebody not familiar with our business.

Mr. EDGAR. How small is small?

Dr. ERICKSON. Well, we are talking about basically relative risks of around two. Maybe I can put this into perspective, taking a little bit of liberty with some data. A few years ago, I was writing a paper on the epidemiology of developmental disorders for nonepidemiologists, and in that paper, I described the thalidomide episode.

Most of the people here are aware of the epidemic of birth defects that were caused by thalidomide, a tranquilizer thought to be innocuous and used widely in Europe in the sixties. When one assembles the data today from Europe, one finds a relative risk of having a baby with a particular type of defect due to thalidomide being 220.

There is a situation where we have a known cause and effect relationship acting through the mothers, an environmental agent, a drug taken by the mothers causing these particular defects.

When you assemble the data, in retrospect now, the relative risk, the risk of mothers who took thalidomide relative to mothers who did not, is 220. We are talking about relative risk of two.

Mrs. **Johnson**. 220 to 2?

Mr. **Edgar**. 220 in thalidomide and 2——

Dr. **Erickson**. In our study.

Mr. **Edgar** [continuing]. I am still not clear on that. 220 to 2, what does that mean?

Dr. **Erickson**. Well, that the risk, relative risk of 2 would imply that the risk is 100 percent higher, two-fold increase in risk. If a defect only occurs in one in 1,000 pregnancies, a two-fold increase in risk or a relative risk of 2 would indicate 2 in 1,000.

Mr. **Edgar**. OK, how many in a thousand increase did you find with spina bifida?

Dr. **Erickson**. Roughly one.

Mr. **Edgar**. One over the control number of one, so it would be two?

Dr. **Erickson**. Roughly.

Mr. **Edgar**. 100 percent increase in spina bifida?

Dr. **Erickson**. In effect, that is what that means, yes.

Mr. **Edgar**. In terms of real numbers, it is very small.

Dr. **Erickson**. Yes, sir.

Mr. **Edgar**. 100 percent higher at risk?

Dr. **Erickson**. Yes, sir.

Mr. **Edgar**. In terms of cleft lips, what are we talking about, one to two?

Dr. **Erickson**. Yes, something on that order. Whereas with the thalidomide example, we are talking 22,000 percent.

Mr. **Edgar**. Right, that is making it much clearer to me in terms of a level. Now, if you focus down just on point C of my comment before with Congressman Daschle, that is, those that the military said were exposed to agent orange, and that is where you got your 100 percent increase, in a sense, from one to two, would that lead you as a scientist to believe that exposure to agent orange in a civilian environment similar to that of a military environment, might lead to a higher, yet significantly small, higher incident of spina bifida, cleft lip, as a result of exposure to agent orange?

Dr. **Erickson**. Well, I think that if one wanted to raise the postulate that the findings in our study reflected a true causal association between agent orange exposure and the defects, and that if in the domestic use of herbicides in this country, there were equivalent exposures, one might expect to see increases in the rates of these defects in the population at large.

There are a lot of ifs that lead up to that.

Mr. **Edgar**. I understand.

As a result of your study of birth defects, do you come to any specific conclusions as to the risk of this particular substance, dioxin used in agent orange or agent orange itself, as to whether or not it in fact has or has not an impact on these birth defects?

Dr. **Erickson**. Only insofar as our index is valid, and we don't know about that, and only insofar as one can make some assumptions about the absolute levels of exposure that these men underwent, we just don't know that, so if you want to say, do we know, does dioxin exposure at some given level cause spina bifida, we just don't know that.

Mr. **Edgar**. What would we need to do to find out the yes-or-no answer to the question, does agent orange cause birth defects?

Dr. **Erickson**. I am not sure you are going to get a better answer than we have been able to get in this study, Mr. Edgar.

Mr. **Edgar**. Yet you just answered my previous question by saying you don't know. Are you suggesting that that is the answer?

Dr. **Erickson**. That may be the answer, yes, sir.

Mr. **Edgar**. Dr. Beach, when do you think the Science Panel's plans for initiating further research with relation to dioxin and birth defects may take place?

Dr. **Beach**. Mr. Chairman, already, the Science Panel has begun to study the very serious questions that have been asked concerning dioxin and birth defects and as indicated, the broader issue of the NIOSH worker studies. Their proposed protocols have only just begun to be looked at by the Science Panel. These will be done as a high priority.

There is a tremendous interest in this, and we will be following it through as a priority. We are going to keep you informed as we get results.

Mr. **Edgar**. I will yield to my colleague, Mrs. Johnson.

Mrs. **Johnson**. I gather from what you have been saying, and I am sorry that I missed all of your testimony but I have read through your written testimony, from your comments and I would conclude that, unless we can create a study in which the participants know the amount of exposure that they experienced, we cannot learn more than your study has given us. Is that a crucial factor?

Is that the one thing that keeps us from being able to answer the questions of the chairman more precisely, the fact that the subjects of the study do not know, nor can tell us what their level of exposure was?

Dr. **Erickson**. I think that is pretty fair. Now, in our study, we did ask veterans whether they believed they were exposed or not. I don't know whether they can really tell us or not, in the sense of we would like to have some, you know, a dioxin meter that we can read what was left over from Vietnam.

We don't have that. We are a long, long way from that.

Mrs. **Johnson**. You have no way of knowing, or there is no evidence that would indicate to you, whether that person had been exposed or not, and if so, how much? Is that true?

Dr. **Erickson**. Not in any precise way, no. We have worked with the Army Agent Orange Task Force to do what we believe is about the best you can do, which is working from military records, documenting troop positions, so on.

Mrs. **Johnson**. Thank you.

Mr. **Edgar**. Any other questions?

Let me have just a couple of minutes with you, and then we will move on.

I am still in a quandary, because I think your study is a pretty good one and generally, we can say to the veterans' population, as it relates to birth defects, given the work we have done on the study, there does not seem to be for overall Vietnam veterans a significant problem, and for those who thought they were exposed, it doesn't seem like there is any higher rate.

For those who were exposed, according to limited records of the military, there were some significant changes in a couple of different areas, and we have the Agent Orange Working Group that will come back to us with additional subject areas, possibly to explore, or to get answers for.

I am still having a little bit of a problem specifically with those veterans who might come to us and say, my child has spina bifida.

My child has a facial birth defect that I believe is caused by exposure to agent orange, and I have gotten this study from the Centers for Disease Control which tells me that I had a 100-percent higher chance of having a child with that kind of a defect, even though, in terms of raw numbers, you and I know that that is a fairly small group.

What do we say to those veterans?

Dr. ERICKSON. I think our study does raise the possibility that a particular birth defect in a particular individual has been related to something that happened in Vietnam.

We can't rule out that possibility, but our feeling, I think I speak for the whole investigative team at CDC, our feeling is that these positive findings that we are focusing on are in our sort of professional opinion more likely to be statistical flukes than indications of real causal associations.

For example, let me tell you a little bit more about spina bifida, to give you an example why we feel that way about that particular defect.

Mr. EDGAR. Statistical flukes is the word that you used?

Dr. ERICKSON. Yes.

Mr. EDGAR. I used the word blip.

Dr. ERICKSON. Spina bifida is a defect of the exposure of the embryonic neural tube. The embryo, there is some folding over of external layers of cells into a tube called the neural tube, and it zips up toward the tail and up toward the head.

If the zipping up doesn't occur properly as it is moving toward the tail, you get spina bifida. As the zipping up is occurring toward the head, the closure doesn't occur properly, the baby is affected with something called anencephaly.

These defects are related embryonically. Epidemiologically, they run in the same families. They often occur together in the same babies.

We did not find any association with anencephaly and the agent orange exposure opportunity indices.

If the association was a strong one, you might reasonably expect to see a similar association with the defect anencephaly. We did not. That moves us away from thinking that this association may be causal.

Mr. EDGAR. Is there any other analysis, for example, a cleft lip and palate, that might indicate the same kind of suspicion that it is a statistical blip?

Dr. ERICKSON. Not quite the same, the same type of information that we put into our thought processes, but a couple of facts are worth mentioning.

First, in our analysis, cleft lip with or without cleft palate occurred more frequently in veterans, excluding Vietnam veterans. I have no idea why that might be so, but it was. That happened in our study data.

Mr. EDGAR. Give me that one again.

Dr. ERICKSON. Veterans of military service, excluding Vietnam veterans——

Mr. EDGAR. Who did not serve in Vietnam?

Dr. ERICKSON [continuing]. Right, were at significantly greater risk of having a baby with cleft lip with or without cleft palate. That is pretty hard to explain why that should be reflecting anything biologic underneath that.

Second, we did, as a routine matter for all of the defect groupings, an analysis which took account of other risk factors for birth defects, risk factors which were chosen by a group of birth defect specialists at CDC prior to data analysis as being potentially important for making inferences about these data.

They were things like alcohol consumption in the mothers and so on. After the analysis of the cleft lip with or without cleft palate data, taking these other factors into account, there was some reduction in the estimated risk, and it was no longer statistically significant.

Mr. EDGAR. One final question.

When you move from one to two, so that you got 100 percent increase, how often in these statistical blips do you move from one to 1.3 or 1.5 as a relationship to moving from 1.1 to 2?

I guess I am wondering, the level of significance here, why wouldn't you have found lower?

Dr. ERICKSON. Almost never exactly one, because that just doesn't happen unless you have massively large samples. In terms of a distribution and an expected distribution of those things or what was realized in our study, I can't give you that off the top of my head, although we would be glad to try to submitting something for the record.

Mr. EDGAR. I am trying to figure out whether it is significant or not. It is real hard to know that, in terms of just moving, 100 percent increase?

Dr. ERICKSON. Yes, Mr. Edgar.

Mr. EDGAR. When you say 100 percent, when you say two, it doesn't strike you quite as hard.

Dr. ERICKSON. Remember, the 220, 22,000 example as well.

Mr. DASCHLE. Mr. Chairman, a couple parting questions. That was the same concern I had when I saw this 2.57 relating to the children after the index child that may have birth defects, and that to me seems significant, and I don't know how to evaluate its significance.

If it is 2.57, if you are saying the two represents 100 percent, are we talking about something greater than 100 percent increase of children following the index child?

Dr. ERICKSON. Yes.

Mr. DASCHLE. We are. Would you then say that that is significant or not?

Dr. ERICKSON. From the point of view of trying to assess whether we think this is an indication of some causal relationship? It is an interesting finding. It is a peculiar one in the sense that this occurred among men who said themselves that they were exposed to agent orange.

Now, in our study analysis of those responses, responses of the individuals about their perceptions of agent orange exposure, we did a special kind of comparison. We made comparisons of the risks for one type of defect relative to all other types of defects.

We didn't make any comparisons directly to the usual control series in our study, that is, parents of babies without defects. We did that for a reason that goes something like this:

Studies such as ours are rife with potential for what we call respondent bias; that is, those people who are the parents of a baby with a birth defect may well have a heightened memory of events, a better recall, maybe even a tendency to overreport things, and in our reviews, our study plans prior to the conduct of the study, we had laid out that we would make this comparison that should minimize this potential for response bias.

Now, we were not able to do that in this particular issue, and I think the only insight I can offer you is, we think it is possible that this particular finding is an indication of some sort of response bias that parents with two or more babies with defects may be more likely to self-report agent orange exposure.

Mr. Daschle. Given the low participation of blacks, do you have any concern about the validity in extrapolating data about blacks in this study, above and beyond what you have in the nonblack population in your study?

Dr. Erickson. Any time you don't reach 100 percent participation, you start to worry a little bit, and overall, we feel that our participation rate was pretty good, and that it would be very difficult for us to miss something substantial because of that.

In terms of black fathers, I don't think we can say that. We were rather disappointed that the participation rate was so low, and our ability to comment on black fathers is hampered to some degree. However, there is not too much reason to suspect that one ought to be concerned on the basis of the occurrence of malformations anyway. That is not a major problem, but we do say we are a bit concerned about that.

Mr. Daschle. Thank you, Mr. Chairman.

Mr. Edgar. Any additional questions? Mrs. Johnson?

Mrs. Johnson. Thank you, Mr. Chairman.

I do want you to, if you would, please, walk us through this 22,000 comparison again. It is very important, especially in talking to people out there about this study, to be able to put the 100 percent and the 22,000 percent in perspective.

When you talk about thalidomide babies, you are saying that women who took thalidomide, versus women who did not take thalidomide, you take over from there.

Dr. Erickson. A relative risk of 220.

Mrs. Johnson. What?

Dr. Erickson. Of 220.

Mrs. Johnson. 220 percent greater risk?

Dr. Erickson. Relative risk of 220, that in a sense can be related back to one, and if you want to put it in a percent increase.

Mrs. **Johnson**. 22,000 percent greater likelihood of having a birth defect baby?

Dr. **Erickson**. No, 220-fold greater likelihood, 220 times, if the rate was one, it becomes 220, you can say that the 22,000-percent increase, depending upon whether you are expressing it in percent or as an absolute multiple.

Mrs. **Johnson**. 220-fold or 22,000 percent more, greater likelihood of having a birth defect child?

Dr. **Erickson**. With the specific type of birth defect.

Mrs. **Johnson**. Thank you.

Mr. **Edgar**. I need to go back and freshen up on my math, because I have always had trouble; and I have repeated this before. How can you have more than 100 percent?

I always thought 100 percent was tops, and then we talk about 150 percent, 22,000 percent. It is hard for me to calculate that with my limited math background, but I appreciate your using that illustration. It is helpful.

Any other questions of these witnesses? Thank you for coming and being with us today.

Mr. **Edgar**. I would like to now call the Office of Technology Assessment, Dr. Michael Gough and Ms. Hellen Gelband.

STATEMENTS OF MICHAEL GOUGH, DIRECTOR OF SPECIAL PROJECTS, HEALTH AND LIFE SCIENCES DIVISION, OFFICE OF TECHNOLOGY ASSESSMENT, AND HELLEN GELBAND, ANALYST, HEALTH PROGRAM, OFFICE OF TECHNOLOGY ASSESSMENT

Mr. **Gough**. I am Michael Gough, Director of Special Projects in the Health and Life Sciences Division in the Office of Technology Assessment. With me is Hellen Gelband, an analyst for the OTA Health Program.

Both of us spend part of our time on the issue of agent orange. I request that our entire written testimony be placed in the record. We will divide our verbal testimony between us this morning, and both of us will be available to respond to questions.

Ms. **Gelband**. The CDC birth defects study was designed and carried out with advice from and review by many members of the scientific community. Knowledge of that review process and OTA's own reading of the report convince us that the basic design and statistical methods used were appropriate, and that there are no major flaws in data analysis.

We fully accept the results of the analyses relating to Vietnam service, but are less certain of the meaning of the results as they relate to agent orange. Our reservations stem mainly from uncertainty about the reliability of the agent orange exposure indices.

The data firmly support the conclusions drawn about the lack of an overall major increase in risk associated with Vietnam service.

The value of this study, as has been the case with the Air Force's Ranch Hand Morbidity Study, an investigation of the men who participated in the fixed wing aircraft herbicide spray program, and the Australian birth defects study, a case control study that investigated Vietnam service as a risk factor for fathering a baby with a birth defect, is to set some upper limits on the risks associated with Vietnam service and possibly agent orange exposure.

The evidence from this study and the Australian birth defects study is consistent, finding no generalized increase in the rate of birth defects associated with Vietnam service.

The Ranch Hand study, which depended on parental recollections and took into account minor birth defects that were not addressed by CDC, found a statistically significant increase in total birth defects in the Ranch Hand group.

The Air Force is currently obtaining medical and birth records to evaluate fully questions of birth outcomes in Ranch Handers and a control group.

The Ranch Hand study is investigating the effects of agent orange, based on the assumption that Ranch Hand personnel were, in fact, exposed. The "Vietnam Experience" is not part of that study, since the comparison group is made up of Vietnam veterans who are similar to Ranch Handers except for their lack of agent orange exposure.

The Air Force expects to have detailed information about the Ranch Hand birth outcomes in December 1984.

Positive findings: The positive findings of the CDC study deserve careful scrutiny. First, there were no positive associations of major birth defects in offspring with service in Vietnam, or with self-reported [yes/no] agent orange exposure.

The three major positive associations—with spina bifida, cleft lip with or without cleft palate, and other neoplasms—were found only with the agent orange exposure opportunity indices. Assuming for the moment that the exposure indices are valid, the meaning of the positive findings still requires interpretation.

The important question is whether those positive findings represent causal associations. The answer to that question involves more than a single finding of statistical significance.

The strength of the association, represented by the relative risk, the biological plausibility of the association, and the consistency of the association with findings from other studies also are important.

Although there are no objective criteria for judging the importance of relative risks, in general, a relative risk of less than 2 is considered relatively small, as we heard from Dr. Erickson.

A relative risk of two means that the defect occurs twice as frequently in the case group as it does in the control group. If a defect usually occurs at a rate of 1 in 1,000, at a relative risk of 2, it would occur at the rate of 2 in 1,000. One of the two could be attributed to the factors at work in the general population, and the one excess case to the factor responsible for the increased risk.

The judgment of what is important, of course, must be tempered by the seriousness of the defect and the magnitude of the incidence rate in the general population.

The relative risks for the categories of birth defects with increased occurrence in this study all are relatively low, and they occur in categories of fairly low incidence in the general population.

The defects, however, particularly spina bifida and other neoplasms, are serious.

The possibility that the associations are simply due to chance must also be considered, but there is no way to know this based on a single study.

The generally accepted level of significance in epidemiology, to which this study adhered, is 0.05, meaning that the probability of the apparent association being due to chance is no more than 5 percent.

At this level, if in fact there were no difference, there is still a 5-percent chance of an association appearing. In other words, in 5 out of 100 analyses, one would expect false positive results.

In this study, with at least two and in most cases three analyses of 96 defects or groups of defects, one would expect some statistically significant findings to occur by chance.

A causal association should make biologic sense and should show consistency among studies. In this case, there are no strong biologic hypotheses linking birth defects with a father's previous exposure to agent orange.

A possible association of agent orange exposure and birth defects was worthy of investigation in part because there are few other compelling hypotheses to test.

OTA has two concerns about the information produced by the CDC birth defects study. First is the low participation rate among other race parents, mainly blacks. CDC acknowledges this weakness, and places the appropriate caveats around the findings in other race participants.

Based on the pilot study, CDC predicted that about 70 percent of eligible case and control parents would participate in the study. The projected 30 percent who would not participate included both parents who could not be located and those who would choose not to participate.

For white case parents, that prediction was reasonably accurate. For the other race subgroup, however, participation was much lower. About 60 percent of other race mothers, and just over 30 percent of other race fathers completed interviews.

The study results, as CDC points out, may be less generalizable to the other race population than are the results for whites to the white population.

Participation by a small percentage of those initially selected raises concern that participants may differ from nonparticipants. The fact of being difficult to locate in itself may indicate that those people are in some way different from those who were located.

Two types of effects of nonparticipation are important. First, having fewer cases and controls than planned decreases the power of the study to detect associations even if they exist. The likelihood of false negative results is increased.

Second, the results might be quite different if the exposure characteristics of the nonparticipants were known. Unfortunately, the possible biases introduced in this way are unknowable, and the analysis is rightly based on the information that is available.

Mr. GOUGH. Our second and more serious concern is doubt about whether the agent orange exposure opportunity indices faithfully reproduce the different exposure histories of veterans.

We emphasize that this concern has no bearing on the most significant finding of the CDC study that Vietnam service is not associated with an increased risk of birth defects, but it is key to the interpretation of defects associated with agent orange.

Since we prepared our review of the CDC study, we have learned more about the assignment of exposure classification. Part of our information was obtained in our role as observers to the Agent Orange Working Group, and that must be held in confidence.

However, without compromising confidentiality, we can provide you the basis for our concern that the exposure opportunity indices may not provide an approximation of relative exposure to agent orange. In our opinion, the likely misclassification prevents the drawing of any conclusions based on the agent orange exposure opportunity indices.

A method to estimate the likelihood of a veteran's having been exposed to agent orange was developed by the Army Agent Orange Task Force. The task force outlined their proposed method in a memorandum to the Science Panel of the Agent Orange Working Group [AOWG] in April 1982.

In essence, that memo said that the Army could identify the units that a veteran served with in Vietnam. The locations of the units could be determined and plotted on maps against recorded uses of agent orange. Men whose units were closer to locations where agent orange was known to have been used would be accorded a higher likelihood of having been exposed to the herbicide.

Last week, we received, as observers to the AOWG, more details of the Army's methods used to assign a veteran to a category in the exposure opportunity index. The methods were presented in a draft to the AOWG, but they are, we understand, essentially what was used in the birth defects study. They provide more detail than the April 1982 memorandum, and they include some subjective judgments of the likelihood of a veteran's being exposed.

Inspection of table 5 of the full report of CDC's birth defects study, a copy of which is attached to our testimonory, illuminates our concerns. The table presents examples of military units that were classified on a scale of 1 to 5, with 1 being minimum opportunities for exposure, and 5 being most numerous opportunities for exposure.

Although the table contains only examples and not a full reporting of classifications, it is noteworthy that infantry/combat arms appear only in the high groups 4 and 5, and noninfantry appear primarily in groups 2 and 3.

Given men who were in the same proximity to spraying, men in combat units were assigned higher exposure opportunity index scores than were men in noncombat units. With the same objective exposure rating, based on time and distance from agent orange use, a combat soldier and a noncombat soldier could be assigned ratings as much as three categories apart, in most cases, actually two categories apart.

In large measure, then, the indices represent service in combat units at least as much as they do exposure to agent orange, and because the distinction between combat and noncombat units plays such an important role in exposure ratings, the true relative agent orange exposures may be entirely obscured.

If this is the case, and we believe it very possibly is, associations with the indices would have no meaning. What makes this such a vexing problem is that there does not exist, nor is there in prospect, a way to validate any exposure index such as those used in this study.

The fact that the two agent orange exposure indices reported in the CDC study agree with each other reasonably well is not evidence that they are valid. It only provides assurance of consistency in assigning ratings given the objective information.

In one index, military records were used to determine the veteran's units and their locations of the units; in the other index, the veteran's recall was the source of information about units he served with and their locations. In either case, information such as "infantry" or "noninfantry" would almost certainly be the same. If both answers were infantry, the subjective decisions would tend to place the veteran in category 4 or 5. If the answers were noninfantry, he would be placed in category 3 or lower. In our opinion, the subjective decisions swamp the other information.

It may be that combat units were more exposed, given identical objective exposure information, but support for that argument is not provided.

We think that there is probably no way to develop a reliable exposure index, and we do not attribute this situation to failure on the part of any individuals or institutions. The best people have tried, with the best information they could develop, without a satisfactory outcome.

The validity or lack of validity of the agent orange exposure opportunity indices does not in any way affect the conclusions about there being associations of birth defects with Vietnam service.

If the indices are invalid, however, the agent orange analyses provide no reliable information either to rule out associations with agent orange or to confirm them.

That is the end of our prepared testimony.

[The Statement of Mr. Gough and Ms. Gelband appears on p. 76.]

Mr. **Edgar**. Thank you.

I refer to on page 9 of your statement, the last sentence, "We think that there is probably no way to develop a reliable exposure index." That is a tough sentence, because your comments are a bit critical of the way in which the index was developed.

Do you have suggestions on how the index could have been or should have been developed that would have been better?

Mr. **Gough**. I anticipated that question, and I have written out some notes.

I would like to answer that question in the context of the planned CDC epidemiologic study, the large study that involves 18,000 veterans, and which also depends on exposure classification, and I would like to say that the methods to be used there are different.

Mr. **Edgar**. Are they better?

Mr. **Gough**. Yes, better in the sense that an effort is being made to identify units which were highly exposed and units which were probably not exposed at all, and the comparisons will made between veterans highly exposed and those not exposed at all, rather than taking every veteran who entered the study, and placing him in one category or another, 5, 4, 3, 2 or 1. So the big study should have a much cleaner difference between exposure and nonexposure.

I don't think that is possible to do anything comparable with the CDC birth defects study. There are too few veterans in that population, 500 in the birth defects study, and if we eliminated people who are in the ambiguous middle group, there would be so few people that no analysis could be done.

Mr. **Edgar**. Would it be accurate to say that the Office of Technology Assessment, while finding two areas of concern; namely, the race differentation and the participation there, and the indices question, which you raised, you found no other problems with the study?

Mr. **Gough**. That is fair. We think it was well done, honestly presented.

Mr. **Edgar**. This is a question I wanted to ask earlier and had not asked, but would there by any need in your opinion in looking at this study to raise a question about why women veterans were not looked at in a special category, who, in fact, after service in Vietnam gave birth to children?

Mr. **Gough**. Yes, I think the reason they were not included in this study was that there were probably so few Vietnam women veterans in the Atlanta area. The analysis would be very hampered by very small numbers.

I think that CDC is planning a study, or at least discussing doing a study, of women Vietnam veterans. I am unsure how much information we'll obtain about the reproductive outcomes.

Mr. **Edgar**. Dr. Erickson, you wish to respond briefly about whether or not a study of women veterans who have had children or are of child-bearing age might be studied?

Dr. **Erickson**. I can make two comments.

First, in our study, the birth defect study was not designed to deal with women veterans for the reasons that Dr. Gough mentioned, although we did ask every mother who participated in the study whether they had been in Vietnam and if she had, what she had done there.

There was one mother who had been in Vietnam service in our study.

Mr. **Bilirakis**. Did she have a child that had defects or did not?

Dr. **Erickson**. She had a child with a defect.

Mr. **Bilirakis**. With defect?

Dr. **Erickson**. The CDC has put together a short outline of a plan for a study of women Vietnam veterans. It was submitted to the Agent Orange Working Group for consideration some time this summer. That is the status of that.

Mr. **Edgar**. While you are still at the mike, Congressman Don Edwards would like to know whether or not it would be possible for you to provide him with a raw copy of the original draft of the birth defect study written before it was sent to the Department of Defense for comparison?

Dr. **Erickson**. Before it was sent to the Department?

Mr. **Edgar**. For their vocabulary changes that were discussed earlier.

Dr. **Erickson**. That particular segment of the study?

Mr. **Edgar**. Is there a raw draft someplace?

Dr. ERICKSON. I am not sure. We can look into that and let you know.

Mr. EDGAR. If you have the material before it was edited, even in terms of vocabulary by the Department of Defense, we would like that transmitted to Congressman Don Edwards' office.

Thank you. I have a number of questions, but I will yield to my colleague, Mr. Bilirakis.

Mr. BILIRAKIS. Thank you, Mr. Chairman.

Mr. Gough and Ms. Gelband, in the first paragraph of your testimony, you say when planning began for the study in 1980, there was no method available for assessing exposure to agent orange in military records.

In the course of planning, such a method was developed, et cetera, et cetera. There is testimony by, I believe, Dr. Erickson, I am not sure, yes, Dr. Erickson, on page 4, where he said Vietnam veteran fathers were given subjective scores by the staff of the Army Agent Orange Task Force reflecting their presumed opportunities for exposure to agent orange.

In evaluating the plan and the study, are you satisfied that even though emphasis, at least I place emphasis on the word "subjective" here, are you satisfied that those scores were legitimate scores?

Mr. GOUGH. No, we are not. There are some objective things we know: the location of 2 company headquarters and that a Ranch Hand airplane passed over that base within a certain number of kilometers, or within a certain number of days. Those are objective.

The subjective decisions had to do with the likelihood of a veteran being actually exposed. The subjective decision is that a member of an infantry unit is more likely to have come in contact with the spray or gotten closer to it than a man who stayed in the fire base. For example, the subjective decision is made that a man in the supply corps or somebody in the artillery unit above the divisional level was less likely exposed.

To my mind, there is no reason to believe that the infantryman would move toward the spray. He might stay in the base, or even go in the other direction, and we think those subjective classifications seriously compromise the agent orange exposure opportunity indices so much so that we wouldn't use them to draw conclusions.

Mr. EDGAR. I think you are generally right in your comment and your suggestion that the ongoing CDC study of more veterans will have better indices. I just wonder whether or not we can take as a fact the statement that the person staying in a fire base as opposed to that of one who is tromping through the jungle areas wouldn't have exposure.

I happen to know of an incident of a veteran in my district who stayed fairly close to the fire base, but he spent a good deal of his time spraying agent orange around the fire base to keep the weeds down.

So I think it would still be a little bit subjective if you came up with a unit tromping around versus somebody who stayed in, and that points to your issue then that it is difficult to get an accurate index this late of exactly who was exposed, and we can do better at it.

Mr. GOUGH. For a veteran in a special category, a chemical corps veteran, who may have sprayed agent orange from a backpack or from a truck, allowances were made for him.

He would be a special case.

Mr. BILIRAKIS. You are satisfied that allowances were made?

Mr. GOUGH. For particular cases, such as chemical corps members, ranch handers, ground and air crew, those allowances were made.

Mr. BILIRAKIS. Your office studies the criteria that was used by these subjective and objective evaluators, and you are basically satisfied that they did the best that they could do under the circumstances, that they were not biased because they are part of the Department of the Army?

Mr. GOUGH. I don't think the bias is because of the Department of the Army. There definitely is a bias as toward assigning higher exposure opportunity numbers to members of combat units. That may be valid, but that idea is not supported in any of these reports, not even discussed.

It is taken as a given that those men would be more highly exposed.

Mr. BILIRAKIS. Did I understand you to say that you think there may have been some bias there, but you think that the bias was—they evaluated them higher, they applied a higher exposure rating rather than a lower?

Mr. GOUGH. It goes both ways. If a man, if a veteran was a member of a combat unit, his chances of being in group 4 or 5, the highest exposed group, are much, much better than it is if he is a member of a noncombat unit.

That is a distinct bias both ways, and that is our concern, the problems those two biases would introduce in the analysis.

We think that it very much compromises the agent orange exposure opportunity indices to the point where they have no validity.

Mr. BILIRAKIS. Would you have any suggestions as to how that could be better done?

Mr. GOUGH. No, but Ms. Gelband would like to say something.

Ms. GELBAND. I think everyone agrees that there are some subjective judgments that have to go into making any exposure opportunity index. The reason that we feel it can't be done to everone's satisfaction maybe is that we know the views of the people involved and true data available.

We know the military records experts and the epidemiologic arguments, and this has been discussed a lot in the Agent Orange Working Group.

It doesn't appear that there is any way to massage this information together to give everyone a feeling that the indices are accurate. When we talk about biases, we are not saying that the people who assigned the ratings were biased. They made decisions based on certain rules that had been developed by the CDC researchers and the AAOTF staff that seemed reasonable to them.

What we are questioning are the subjective rules for assigning those ratings.

Mr. BILIRAKIS. I believe would be good if you explained the functions of the Office of Technology Assessment just for the record. You are an arm of the Congress of the United States?

Mr. GOUGH. That is right.

Mr. BILIRAKIS. What is the function of the Office, generally?

Mr. GOUGH. The general function of the Office of Technology Assessment is to provide Congress information about technical issues, and to oftentimes try to provide a glimpse forward about the impact of new technologies that are being introduced.

Our role in agent orange is a result of Public Law 96-151, which mandated that the Veterans' Administration do an epidemiological study, and in that law, it was mandated that OTA would review the protocol that study and monitor the conduct of that study.

Our involvement now in the CDC birth defects study primarily came from a request from Senator Cranston to review that study, and also letters from Congressmen Montgomery, Hammerschmidt, and Edgar requesting that they receive a copy of the review.

Mr. BILIRAKIS. And to whom do you and your Director, Mr. Gibbons, answer?

Mr. GOUGH. To the Technology Assessment Board's, six Congressmen, six Senators, three Democrats and three Republicans. The chairmanship alternates between the Houses. It is currently in the House, and Morris Udall is the chairman and Ted Stevens of Alaska is the vice chairman. They generally meet monthly to review what we have done.

Mr. BILIRAKIS. Thank you, Mr. Chairman.

Thank you very much.

Mr. EDGAR. Mr. Daschle, do you have any questions?

Mr. DASCHLE. I just have a couple.

I would go back to my questions to the earlier panel. The last statement in your statement seems to be the one that is most perplexing to me. The agent orange analyses provide no reliable information either to rule out associations with agent orange or to confirm them.

Are we any closer to ruling out or confirming any association in spite of the problems you have described with the indices as a result of this study?

Mr. GOUGH. With respect to agent orange, I don't think so, because we consider those exposure opportunity indices to be very seriously flawed.

Mr. DASCHLE. And yet, in a question just a moment ago, you cannot provide a recommendation for better indices?

Mr. GOUGH. Right. There are some things that simply cannot be done, and I will give you an example. We can shoot a rocket that way [up], 50 miles in a couple of seconds, but we can't go that way [down], even a few feet in a couple of minutes.

There are a few things that are beyond our capability, and working with a group of 500 or so veterans and using the information we have available about agent orange exposure, I think it is probably impossible to develop exposure opportunity criteria which will be satisfying to all parties.

Mr. DASCHLE. Would you suggest to this committee that we are spinning our wheels in a sense?

Mr. GOUGH. No, sir, I think the overall conclusion that service in Vietnam is not associated with increased risk of birth defects is a very important finding, and should provide some assurance that veterans are not at an increased risk.

We gave it our best shot, but we think that it wasn't quite good enough, and unfortunately, we don't know how to do it better. There are lots of smart people in the world, though, and somebody else might know how to do it better.

Mr. **Daschle**. To me, that is extraordinarily significant. I am delighted with the findings, and very pleased with that. If we can even say that serving in Vietnam does not show significant statistical chances for increases in birth defects, that is saying a great deal.

It is disturbing to me that what we are talking about here is agent orange, not Vietnam, and we are not any farther along in that regard.

One other question related to a question I asked earlier, and that is, with regard to the significantly higher numbers of children with birth defects were born after the index baby.

The number I am given is 2.57. What would OTA say about that? That to me, as I look at all the numbers, that is one of the highest numbers in all of the numbers I have seen in the report, and there seems to be, the earlier panel indicated there was significance to that, but that was called unique.

How would you describe this unique factor?

Mr. **Gough**. The number 2.57 is a ratio between the frequency of mothers whose husbands were exposed and who had a second baby with a birth defect divided by the frequency of mothers whose husbands were not exposed and who had a second baby with a birth defect. The ratio is derived from small numbers. The numerator is 7.

Given these small numbers, most people would have reservation about the significance, and I fully concur with Dr. Erickson's remarks, that selective recall may have entered into that.

A family who experienced the birth of two children with birth defects, searching back in their memories for things, may recall more accurately that the father had been exposed in Vietnam than the parents of a child with birth defects who had other children that didn't suffer birth defects.

I think certainly we should point out that the number is worthy of consideration, but it may be a product of a lot of factors, in addition to actually an increased risk.

Mr. **Daschle**. If that is significant or potentially so, one would want to find out whether what you suggest is merely a guess, or whether it might have some statistical significance. It appears in a sense, I don't want to use the word "rationalizing," but explaining away the statistical significance without much more than a guess.

Is there any interest in pursuing this, as to a more significant explanation?

Ms. **Gelband**. 2.57 just is not very big in an epidemiologic study like this.

Mr. **Gough**. It is in this study.

Ms. **Gelband**. Perhaps if we had some really strong positive findings in this study, it wouldn't look so big. Epidemiologic studies are not generally sensitive enough to reliably detect anything lower than about 2—2.5, when you have looked at enough literature, is not very high, and the numbers on which the 2.57 is based are very small.

You would be hard pressed to find enough people on which to do a more indepth study of this topic. To back up a bit, epidemiologic studies all rely on statistical inferences and they are very limited in what they can say.

They are designed to look at and describe populations which this study does, but as you start getting closer and closer to the individual, the studies become less and less useful.

Mr. **Daschle**. Well, I thank you. I thank the chairman. I would like to say one thing for the record that is probably as appropriate to be said here today as anytime I can think.

It is coincidental, but important, I think, in noting the coincidence that today on the floor it appears that a conference report on our compensation bill, 1961, may come up for final consideration.

It is a good compromise, and I think that it demonstrates the dedication that this committee has shown to finding some solution to that part of the problem.

It would not have been possible without the support of this subcommittee and the chairman of the subcommittee, and the subcommittee chaired by Congressman Doug Applegate, and most importantly, our own chairman of the Veterans' Affairs Committee and the ranking member, and of course, the staff.

And I may not have a chance any other time this year to express my deep appreciation to this committee, and to all of its members, for the kind of support and consideration they have given, and thank you for the time.

Mr. **Edgar**. I appreciate that. Your leadership has been very helpful. I can't remember any 2-year period where the issue of agent orange has received as much attention and notice as the last 2 years, when we were able to shift the study to the CDC for some impartial examination, and for this study to come out.

We have made some good strides and perhaps we are increasing the level of understanding about the issue a little better.

I would like to yield for one minor question to our counsel.

Mr. **McDonell**. A twofold question, one, does the EOI data support the self-reported agent orange exposure data, as far as those that said they were exposed versus what the Army said were exposed?

Mr. **Gough**. I can't answer that question. Let me point out however, that using veterans' recollection of their having been exposed or not exposed was examined as a risk factor. There was no association found between the veterans' recollection and any birth defect. CDC did that analysis.

I don't know if they did the comparison you are asking about, and if they did, I can't comment on it.

Mr. **McDonell**. Dr. Erickson, do you know if they did?

Dr. **Erickson**. Yes, we made that comparison. You can find it in table 41 on page 123 of our large report. There was some degree of correlation.

Mr. **McDonell**. There was a correlation?

Dr. **Erickson**. Some degree, nothing real striking.

Mr. **Edgar**. One final question.

You state in your testimony that in your role as observers to the Agent Orange Working Group, you cannot compromise the confidentiality of the group. Could you explain the rules imposed and the limits that have been placed on you?

Mr. GOUGH. Yes, the group is an executive branch function. After passage of Public Law 96-151, Joan Z. Bernstein, who at that time was the general counsel to, it was HEW in those days, invited OTA to come to those meetings as an observer. She asked me as OTA representative, to sign an agreement that I would treat the discussions of material at that meeting in confidence. I think that probably all the executive branch agencies do the same thing. I have treated those discussions in confidence.

I would like to add that we have always been cordially treated and we get along very well with the people in the working group. Being observers has been very useful to us.

Mr. EDGAR. You mean the executive and legislative branches can work together?

Mr. GOUGH. The members of AOWG can work with Hellen and me.

Mr. EDGAR. With that as the closing comment for this hearing, let me thank everyone for participating.

The subcommittee stands adjourned.

[The charters appear on pages 86 and 89.]

[Whereupon, at 12:30 p.m., the subcommittee was adjourned.]

APPENDIX

Congress of the United States
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WASHINGTON, D.C. 20510

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SEP 25 1984

September 24, 1984

The Honorable John Paul Hammerschmidt
Ranking Minority Member
Committee on Veterans' Affairs
U.S. House of Representatives
Washington, D.C. 20515

Dear Congressman Hammerschmidt:

Enclosed is OTA's review of the Centers for Disease Control (CDC) study, "Vietnam Veterans' Risks for Fathering Babies with Birth Defects." We find that CDC has conducted the study according to good scientific practice, and has thoroughly analyzed and honestly presented the results. This study, consistent with information from other studies, provides some assurance that there is no overall increase in the occurrence of birth defects in children of Vietnam veterans or those exposed to Agent Orange, compared with other veterans and with non-veterans. The statistically significant associations that were found between Agent Orange exposure and individual defects are of small magnitude and may be due to chance. Nevertheless, they are of some continuing concern.

The Vietnam Experience and Agent Orange studies, now under way at CDC, will provide additional information about birth defects and other aspects of reproductive health. A study planned by NIOSH will examine the reproductive health of workers in two plants at which chemicals contaminated with dioxin were produced, and the Air Force is continuing to gather information about reproductive health in the Ranch Hand population. These efforts are exploiting the most promising sources of data about birth defects and other aspects of reproductive health and their possible relationship to Vietnam service and Agent Orange exposure. At this time we are unaware of any other promising research opportunities that would contribute substantially to the knowledge base.

If you have any questions about the OTA review or related matters, please call on me, or Michael Gough or Hellen Gelband of the OTA Health Program at 6-2070.

Sincerely,

Jack Gibbons

John H. Gibbons

Enclosure

STAFF MEMO

REVIEW

The Centers for Disease Control Study

"VIETNAM VETERANS' RISKS FOR FATHERING BABIES WITH BIRTH DEFECTS

September 1984

Prepared by the Health Program
Office of Technology Assessment
United States Congress

This OTA Staff Memorandum has neither been reviewed
nor approved by the Technology Assessment Board.

Office of Technology Assessment Review of the Centers for Disease Control Study:

"VIETNAM VETERANS' RISKS FOR FATHERING BABIES WITH BIRTH DEFECTS"

Purpose of the Study

The Centers for Disease Control (CDC) undertook this study to find out whether babies born to male Vietnam veterans are more likely to have major structural birth defects than are babies born to men who did not serve in Vietnam. When planning began for the study, in 1980, there was no method available for assessing exposure to Agent Orange through military records. During the course of planning, however, such a method was developed, and CDC added an "Agent Orange hypothesis" that addressed the question: Is the occurrence of major structural birth defects associated with the father's level of exposure to Agent Orange in Vietnam?

This study was designed and carried out with extensive advice and review by members of the scientific community. Knowledge of that review process and OTA's own reading of the report convince us that the methods used were appropriate, and that there were no major flaws in data analysis. An article describing the study and the major findings was published in the Journal of the American Medical Association (August 17, 1984; Vol 252, No. 7, pages 903-912), and a detailed report of the entire study was made available to OTA by CDC. Both the report and the article underwent review by many scientists. An editorial, prepared by a representative of the American Medical Association, accompanied the article.

This OTA review, based on both the journal article and the full report, concentrates on the interpretation of findings, how they fit with findings from other studies, and their implications for future research.

Findings

The study examined the possibility that the frequency of all major structural birth defects had been increased by Vietnam service of Agent Orange exposure, and the possibility that one or more of 95 specific birth defects or related classes of defects had been increased in frequency. Vietnam veterans did not have an increased risk for fathering babies with all birth defects combined compared with other veterans who did not go to Vietnam, or compared with non-veterans. No associations were detected among the group of men who said they had been exposed to Agent Orange. There also was no significant trend of increasing risk with increasing Agent Orange exposure as measured in either of two Agent Orange Exposure Opportunity Indices. Among individual defects or categories of defects three important statistically significant associations were found. The associations were all with increasing exposure to Agent Orange as measured in one or both Agent Orange Exposure Indices. That type of association is equivalent to a "dose-response" relationship, meaning that the outcome is systematically more or less common with increasing dose.

There was a tendency for increased risk of spina bifida with higher values on both Agent Orange Exposure Opportunity Indices. Cleft lip with or without cleft palate was positively associated with one of the indices, but not the other. Cleft lip was also associated with fathers who are veterans but did not serve in Vietnam. The class "other neoplasms," which includes all the serious congenital tumors, was associated with increasing values on one Agent Orange Exposure Opportunity Index.

Each of the three effects is "statistically significant." However, a few "false positive findings" would be expected to arise by chance. Whether these three effects are true or false postives cannot be known. This issue is discussed in CDC's report, and in this review in the "Discussion" section. The magnitude of each association is relatively small, in epidemiologic terms. The associations themselves account for a relatively small number of cases of defects, if indeed they are not chance associations.

Meaning of the Results

This study is the most powerful investigation of birth defects in relation to Vietnam service and Agent Orange to date, and probably the most powerful possible of this type in the United States. The value of this study, as has been the case with the Ranch Hand Morbidity Study and the Australian birth defects study, is to set some upper limits on the risks associated with Vietnam service and Agent Orange exposure. The evidence from this study and the Australian study is consistent, finding no generalized increase in the rate of birth defects associated with Vietnam service or with Agent Orange exposure. The Ranch Hand study, which depended on parental recollections and considered minor birth defects that were not included by CDC, found a statistically significant increase in total birth defects in the Ranch Hand group. The Air Force is currently obtaining medical and birth records to fully evaluate questions of birth outcomes in their population.

There is no way to detect very small increases overall or even moderate increases in most individual defects, however, through epidemiologic studies. Nevertheless, the studies show that there is no increased overall risk of serious birth defects and provides reassurance that if there are any increases in particular defects, the increases are small.

Study Design

CDC used a "case-control" study design, a commonly-used epidemiologic approach to questions such as those addressed in this study. The study began by assembling a "case group," babies born with birth defects, and a "control group," babies born without such defects during the period 1968-1980. The Metropolitan Atlanta Congenital Defects Program, through which the children with birth defects were identified, is the only such registry in the country that was in operation during the period that most Vietnam veterans were having children. It is essentially impossible to retrospectively create such a registry.

Mothers and fathers of case and control babies were then interviewed and the fathers categorized as to their military experience: they were either 1) non-veterans; 2) veterans who had not served in Vietnam; or 3) Vietnam veterans.

Agent Orange status was determined in three different ways. First, fathers were asked whether they thought they had been exposed. Second, the Army Agent Orange Task Force (AAOTF), by extracting information from each father's military records and using the information about where and when Agent Orange was used, made a judgment about each man's exposure, on a scale of 1-5, with 1 being minimal or no opportunity for exposure and 5 being many opportunities for exposure or opportunities for heavy exposure. Third, the fathers were questioned about where they had been and what they had done in Vietnam, and that information was provided to the AAOTF. Based on that information and the data about Agent Orange use, the AAOTF again rated each man on a scale of 1-5. The two AAOTF ratings were independent, and the individuals who made the ratings did not know the identities of the men or their status as fathers of cases or controls when evaluating exposures.

The analysis of data from case-control studies is conceptually simple: the frequency of suspected "risk factors" in the case group is compared with the frequency in the control group. A higher (or lower) frequency in the case group indicates that the outcome under study, in this case birth defects, is "associated with" the risk factor, in this case either 1) serving in Vietnam, or 2) being exposed to agent orange. The actual analysis was a good deal more sophisticated than simply comparing percentages. For example, because birth defects are known to occur with different frequencies in different race and socioeconomic groups, and because there are trends in the occurrence of birth defects over time, it is usual to take these factors into account when designing a study and analyzing the results. CDC carried out three levels of analysis, "stratifying" the data to greater degrees in the second and third analyses to look for effects of larger and larger numbers of potential associations.

An association does not necessarily connote a causal relationship between the risk factor and the outcome. The analysis is based on the probability of events occurring by chance. As results become more and more different from those predicted by chance, it becomes more likely that some other factor or factors explain the pattern of occurrence. Even extreme results, however, can be expected to occur by chance once in a while.

Aside from the question of probability, associations that show up in the analysis may actually be due to some other, unidentified factor that is associated with both the "risk factor" and the outcome. In the area of birth defects where so little is known about causes, this possibility deserves careful consideration when assessing the results of the study.

Hypotheses Tested

For each of the 96 defects or groups of defects, four hypotheses were investigated:

1. Whether the risks of veterans (excluding Vietnam veterans) for fathering babies with defects differs from that of non-veterans. The reason for investigating this question is because veterans tend to be healthier than other men, and it was thought that this might extend to reproductive health as well.
2. Whether the risk of Vietnam veterans fathering children with birth defects differs from that of other men (both other veterans and non-veterans).
3. Whether men who said they had been exposed to Agent Orange had increased risks of fathering children with birth defects than did men who were in Vietnam but did not think they had been exposed.
4. Whether the risk of fathering a child with a birth defect was related to scores (ranging from 1 to 5 with increasing exposure) on two "Agent Orange Exposure Opportunity Indices."

Case Babies. Case group babies were a subset of all babies registered in the Metropolitan Atlanta Congenital Defects Program (MACDP), who were born between 1968 and 1980, inclusive. All liveborn or stillborn babies with serious or major defects were considered eligible. The guidelines used by CDC to select serious and major defects were:

> ...those [defects] that affect survival, require substantial medical care, result in marked physical or psychological handicaps, or interfere with a baby's prospects for a productive and fulfilling life."

It is certainly these types of defects that concern parents and society.

The MACDP, a unique resource in the country, attempts to register all babies born to mothers living in the Atlanta area. The registry began in 1967, sponsored by Emory University School of Medicine, the Georgia Mental Health

Institute, and CDC. CDC is responsible for running the program. The feature that distinguishes this registry is that it attempts to make a complete accounting of all birth defects in a defined population. To the extent that registration is complete, incidence rates for birth defects can be calculated, and there should be no biases in the data. Bias may occur in registries that count babies born only in specific hospitals, for instance, if the hospitals draw patients of certain socioeconomic or racial groups.

Out of about 13,000 babies registered during the study period, 7133 were eligible for the study, based on the defects or combinations of defects considered major or serious.

Control Babies. Control group babies were chosen from among the 323,421 liveborn babies born to mothers in the metropolitan Atlanta area from 1968 to 1980, the same time period during which case babies were born. Initially, 6,677 controls were selected through a "stratified random sample." The "strata" on which controls were frequency matched with cases were: race, year, quarter of birth, and hospital of birth. This means that within the cases and controls, there were the same proportions of whites and other races; the same proportions from each time period; and the same proportions born in each of the 10 hospitals in the area.

Locating Parents of Babies

Locating and securing the cooperation of individuals chosen for this type of study is the most difficult and in many ways most unpredictable part of the task.

Initially, information about each baby's parents was abstracted from birth certificates for controls, or from the MACDP case record forms for cases. The baby's date of birth, and the mother's name and address at the time of the birth were available for all babies. The mother's maiden name, the father's name, mother's and father's birth dates, father's occupation, and mother's social security number (beginning with 1974, when the MACDP began recording the Social Security Number) were abstracted, but coverage of those items was not complete. In particular, the father's name was more often available on birth certificates than on MACDP forms. Because of that difference, birth certificates were sought for all case babies as well as control babies to eliminate a possible bias in finding parents.

CDC used a variety of sources for locating parents starting with the information available from birth certificates and MACDP records. Sources of current addresses included: the Internal Revenue Service for those mothers whose Social Security Numbers were known; telephone company alphabetic and geographic directories; the postal service; the Georgia Department of Public Safety (for driver's licenses) and other motor vehicle bureaus; credit bureaus; relatives and former neighbors; marriage licenses; the public housing authority in Atlanta; and the Georgia Human Resources Department. Tracing people, especially from addresses as old as 14 or 15 years, is much like detective work. Leads are followed until a person thought to be the parent is located. If the match between parent and child is confirmed the trail ends; if it is a mismatch the search continues.

Participation

Based on the pilot study, CDC predicted that about 70% of eligible case and control parents would participate in the study. The 30% losses include both parents not locatable and those who would choose not to participate. For white case parents, that prediction was reasonably accurate. For the "other race" subgroup, however, participation was much lower. About 60% of other race mothers, and just over 30% of other race fathers completed interviews. The study results, as CDC points out, may be less generalizable to the other race population than are the results for whites to the white population.

Participation by a small percentage of those initially selected raises concern that participants may differ from non-participants. The fact of being difficult to locate in itself reveals that those people are in some way "different" from those who were located. If those differences are systematically associated with exposures, in this case Vietnam service or exposure to Agent Orange, the results of the study may be influenced. Most of the non-participants in this study were the ones never located. A smaller number declined to take part.

Two types of effects of non-participation are important. First, having fewer cases and controls than planned decreases the power of the study to detect associations even if they exist. The likelihood of "false negative" results is increased. Second, the results might be quite different, changing in either direction, if the exposure characteristics of the non-participants were known. Unfortunately, the possible biases introduced in this way are unknowable, and the analysis is rightly based on the information that is available.

Analysis

The data were analyzed at three levels of detail, each incorporating larger numbers of variables. The analytic method used is "conditional logistic regression," a method which allows consideration of more than one factor simultaneously. In other words, the differences in outcomes seen between cases and controls that are explainable by the "adjustment factors" can be filtered out, exposing the amount of the difference associated with other factors, importantly, one hopes, the factors being studied. Adjustment factors are such things as the amount of education that a mother has had. Although there is no biological effect associated with amount of education, it is well known that more poorly educated mothers tend to have poorer birth outcomes than mothers with more education. The possible mechanisms through which the effect might be manifest are several. Education could lead to better nutrition, better medical care, less smoking, or other lifestyle differences. If, for some reason, mothers of case babies were consistently more poorly educated than were mothers of control babies, and this were not factored into the analysis, the possible association with Vietnam service or Agent Orange exposure might appear to be obscured or strengthened.

CDC's basic analyses consider no potential confounding variables except the three stratifying factors — period of birth, race, and hospital of birth. The next level, the primary analysis, adjusted for four additional adjustment factors, each of which is known to be associated with, not necessarily causally, the risk of birth defects: maternal age, maternal education, maternal alcohol consumption, and the occurrence of birth defects in first-degree relatives of the index babies. In the third level of analysis, the secondary analysis, 108 covariables were considered, such as health conditions of the parents; drugs, vitamins, and medical procedures; smoking and drinking habits of parents; and occupation of parents. In general, there were no important differences among the results of the three sets of analyses. The data presented in the JAMA article are from the basic analysis.

Discussion

OTA finds that the CDC birth defects study represents, from a practical perspective, the best effort possible toward investigating the potential excess risks of Vietnam veterans fathering babies with birth defects. It also has addressed as thoroughly as possible in this type of study the question of exposure to Agent Orange and its potential attendant risks for birth defects. The data firmly support the conclusions drawn about the lack of an overall major increase in risk, and those concerning specific defects.

The one concern about the information produced by the study is the low participation rate among other race parents. CDC acknowledges this weakness, and places the appropriate caveats around the findings in other race participants. On the positive side of this, however, there is no biological reason to suppose that the effect of Vietnam service or Agent Orange exposure would be different among whites and non-whites in the risk of fathering children with birth defects.

Positive Findings

The positive findings of the study deserve careful scrutiny. The important question is whether those positive associations represent causative associations. The answer to that question involves more than a simple finding of statistical significance. Other aspects to consider include: the magnitude of the excess risk, which indicates the size of the excess; the biological plausibility of the association; and consistency of the association with findings from other studies.

An initial dichotomy of possible explanations for positive findings is: 1) that there is a true association, causal or not causal, between the risk factor and the outcome; or 2) that the positive finding is a chance event, explainable within the limits of probability, and there is in fact no association. Under the first explanation, the association could be either causal or secondary. A secondary association means that both the exposure and the outcome are independently associated with some third, unidentified factor. An example is an association of heavy drinking with lung cancer. While drinking does not cause lung cancer, both heavy drinking and lung cancer are associated with cigarette smoking. If one does not take into account smoking habits in studies of lung cancer, an association with drinking would appear. If the true causative factor is unknown, however, it cannot be accounted for in the analysis, and the association will not be explainable by other factors.

A causal association should make biologic sense and should show consistency among studies. An important point even about causal associations is that, particularly in an area such as birth defects, a single cause will only in very rare instances be the cause of all cases of a specific defect (a well-known example is the teratogenic effect that thalidomide had on developing fetuses, causing focomelia, a defect almost never encountered in the general population). To illustrate, an odds ratio (or relative risk) of 2.0 means that the defect is twice as frequent in those with the risk factor being investigated compared with those who do not have the risk factor. If a given defect occurs at a rate of 1 per 1,000 in those without the risk factor, it would occur at a rate of 2 per 1,000 in those with the risk factor. The excess would be 1 case, since 1 case would be expected even without the risk factor. In that hypothetical example, 50 percent of the defects among those with the risk factor could be attributed to the risk factor. The remainder presumably are due to other causal factors.

Although there are no objective criteria for judging the importance of odds ratios, in general an odds ratio of less than 2.0 is considered relatively unimportant. This judgement, of course, must be tempered by the seriousness of the defect and the magnitude of the incidence rate in the general population, or in the population without the risk factor. For something that occurs at a very high rate, a two-fold increase would contribute a large excess, in absolute numbers.

The odds ratios for the positive results in this study are relatively low. The positive results all occur in categories of fairly low incidence, as well, so the absolute number of the excess is small. The defects, however, particularly spina bifida and other neoplasms, are serious. Though there is no plausible biological explanation for them involving the father, in general their causes are unknown. However, because alternate explanations are not evident, they must be considered at least as possible causal associations.

The possibility that the associations are simply due to chance must also be considered, but there is no way to knowing this based on a single study. The generally accepted level of significance in epidemiology, to which this study adhered, is 0.05, meaning that the probability of the apparent association being due to chance is no more than 5 percent. At this level, if in fact there were no difference, there is still a 5 percent chance of an association appearing. In other words, in 5 out of 100 analyses, one would expect "false positive" results. In this study, with at least two and in most cases three analyses of 96 defects or groups of defects, one would expect some statistically significant findings to occur simply by chance.

Future Research

OTA is aware of three major studies either ongoing or in planning that will contribute information about the possible effects of Agent Orange on the reproductive health of U.S. veterans. These are the Ranch Hand morbidity study follow-up, the mandated studies of the Vietnam experience and Agent Orange now underway at CDC, and a study well along in planning by the National Institute of Occupational Safety and Health (NIOSH) of workers in their "dioxin registry." Besides looking at birth defects, these studies also are addressing other aspects of reproductive health.

The Ranch Hand morbidity study results that were published in February 1984 reported a statistically significant difference in the total rate of birth defects. The major contributor to the excess reported by Ranch Hands was "skin anomalies," including birth marks. When those defects were removed from consideration, the significant association between being a Ranch Hand and excess birth defects was diminished to a suggestive, but not significant, association. Because the CDC study did not include minor birth defects, this study brings no information to bear on the question of a possible association between them and Vietnam service. The Ranch Hand morbidity study also found suggestive differences in rates of learning disabilities and neonatal deaths. These results were based on reports of parents, and not on medical or vital records. The Air Force is currently obtaining medical and vital records to verify diagnoses, and expects to produce a detailed analysis by the end of 1984.

The Vietnam Experience and Agent Orange studies mandated in public law 96-151, being carried out by CDC, will collect information about birth defects and other aspects of reproductive health, e.g. infertility, stillbirths, and miscarriages. The information will come only from interviews of men, however, and there are no plans to obtain birth certificates or medical records. That is the most reasonable approach for that study, which is designed to look broadly at the health of Vietnam veterans and those exposed to Agent Orange.

NIOSH has developed a protocol to study the reproductive health of workers at two plants where chemicals contaminated with dioxin were produced. The objective of the study is to "determine if occupational exposure to dioxin...is associated with decreased fertility, spontaneous abortions, stillbirths or congenital malformations in the offspring of male workers." NIOSH states that up to 447 employees will be questioned, a fairly small number. Information will be collected from workers and their spouses, and birth, fetal death, and infant death certificates will be collected for verification of reproductive outcomes. The study will not have sufficient power to find any but extremely large increases in overall birth defect rates, but it should be sensitive enough to detect moderate increases in rates of spontaneous abortions.

None of these studies will be as powerful as the CDC birth defects study. The Australian study, because of the small number of veteran fathers, also had less power than does this study to detect the effects of Vietnam service. The NIOSH effort has the advantage of studying men known with greater certainty to have been exposed to dioxin than do any of the studies of Vietnam veterans.

There are no other registries in the United States comparable to the MACDP. The type of study done by CDC cannot be replicated using another data base, and the MACDP data base has been exhausted. It appears that there are no attractive opportunities for epidemiologic studies of Vietnam veterans reproductive health that are not already being pursued.

If the NIOSH study produces suggestive findings, the potential exists to study more workers in the registry. NIOSH has sought to include all people in the registry who worked in chemical production plants where dioxin was present. That resource is just beginning to be used for studies, and there is scope for further study of those individuals.

OTA does not find justification for initiating more studies at this time, given the limited populations appropriate for such investigations, and the fact that none of the studies to date has produced alarming findings. The findings have been suggestive, and to the extent they can be pursued, that is being done.

It might be desirable to solicit ideas from the research community about possible additional studies. Ideas should be critically evaluated by comparing possible outcomes with the studies already completed and those ongoing. Considering the baselines already established, only those which would add significantly to the information base should be undertaken.

ALAN K. SIMPSON, WYO., CHAIRMAN

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United States Senate
COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, D.C. 20510

August 15, 1984

Dr. Edward N. Brandt, Jr.
Assistant Secretary for Health
Department of Health and Human
  Services
Washington, D.C. 20201

Dear Dr. Brandt,

As you know, the Centers for Disease Control has completed its study entitled "Vietnam Veterans' Risks for Fathering Babies Born with Birth Defects".

As the Ranking Minority Member of the Senate Veterans' Affairs Committee, I am writing to request that the Science Panel of the Agent Orange Working Group review and comment on this report. In particular, I would appreciate the Panel's evaluation of the statistical power of the study, both with reference to the study's overall conclusions as well as with reference to specific findings which relate to Vietnam veterans most likely to have been exposed to Agent Orange having a higher risk of fathering babies with certain birth defects. In addition, I would appreciate your evaluation of each finding which shows any statistically significant association to Vietnam service or likelihood of exposure and of the data relating to an association between a veteran having contracted malaria in Vietnam and fathering a baby with a sex organ birth defect.

In addition to commenting on the study itself, I would very much appreciate receiving the Panel's views regarding the need for further research on the issue of birth defects related to exposure to dioxin. In this regard, I understand that a proposal may be coming forward from CDC to carry out a study of birth outcomes among the production workers listed in the NIOSH registry. I would appreciate hearing more about that study, its prospects for funding, and the timetable for its completion. In view of the CDC study findings with respect to certain findings of increased risks associated with Agent Orange exposure, I urge that every effort be made to expedite this NIOSH-registry study.

Also, I would appreciate receiving the views of the full Working Group on what steps the Federal Government might take, either now or during the pendency of further research, to assist Vietnam veterans who have children with birth defects or who are concerned about the possibility of conceiving a child with birth defects.

As you know, I highly value the Working Group and Science Panel's views, especially the Panel's reviews of studies and surveys related to the health effects of exposure to phenoxy herbicides. I look forward to their opinion and perspective on the CDC study.

With best wishes,

Sincerely,

Alan Cranston

Alan Cranston
Ranking Minority Member

DEPARTMENT OF HEALTH & HUMAN SERVICES Secretary

D.C. 20201

REC'D

SEP 28 1984

The Honorable Alan Cranston
Committee on Veterans' Affairs
United States Senate
Washington, DC 20510

Dear Senator Cranston:

This is in further reply to your letter of August 15 regarding several issues relating to dioxin and birth defects.

One of your specific requests was that the Science Panel of the Agent Orange Working Group (AOWG) review and comment on the Centers for Disease Control's (CDC) study entitled "Vietnam Veterans' Risks for Fathering Babies Born with Birth Defects."

This study has been reviewed extensively by several groups of prominent experts. In accordance with the AOWG review procedures, the CDC Birth Defects Study was reviewed by the AOWG Science Panel for adequacy of design before the study was undertaken. After the study was completed, the results were reviewed by the Advisory Committee on Special Studies Relating to the Possible Long-Term Effects of Phenoxy Herbicides and Contaminants. In addition, independent reviews of the completed study were performed by the Journal of the American Medical Association (JAMA) before a summary article about the study was accepted for publication. These reviews were thorough and rigorous. Copies of reviews by the Advisory Committee and by JAMA reviewers, along with CDC's replies, are enclosed. For your information, a copy of the comprehensive study report is also enclosed.

Because of the extensive reviews already performed, the AOWG, at its meeting on September 20, 1984, determined that further review by its Science Panel was neither warranted nor necessary.

The CDC study of birth defects is the largest case-control of its type ever conducted. As you know, the study revealed that Vietnam veterans were not at an increased risk of fathering babies with serious structural birth defects. An editorial note in the Mortality and Morbidity Weekly Report of August 17, 1984, commented on the study:

> The most important conclusion to be drawn from this study is that the data collected contain no evidence to indicate that Vietnam veterans have had a greater risk than other men for fathering babies with defects when all types of serious structural birth defects are combined. This study cannot prove that some factor associated with service in Vietnam was or was not associated with the occurrence of rare types of defects, defects in the babies of selected individuals, or

> defects in the babies of small groups of veterans. The conclusion, however, that Vietnam veterans in general have not fathered, at higher rates than other men, babies with defects when all types of birth defects are combined is based on relatively strong evidence. . .

You do raise an important question about whether there is a need for further research on the relationship between dioxin and birth defects. I have directed the Science Panel of the AOWG to give rigorous consideration to this question. The Science Panel's Subcommittee on Research Agenda has already begun to examine this issue. We will keep you informed of their findings.

An assessment by the Subcommittee on Research Agenda will consider the other sources of data, from which research on serious birth defects could be performed, beyond CDC's Atlanta registry--the basis for the Birth Defects Study; however, pilot studies would be required to determine the feasibility of using these sources. If found feasible, a study based on one or more of these data sets might require substantial time and resources to complete.

The potential for further studies presently rests with CDC's Agent Orange Projects Group which is conducting the epidemiologic studies mandated by Public Law 96-151. Veterans who participate in these studies, the Agent Orange Exposure Study and the Vietnam Experience Study, will be questioned about the occurrence of birth defects in their children. CDC will pay special attention to those defects which were found to be significant in the Birth Defects Study. Even so, it would be nearly impossible to study serious birth defects in a manner as detailed as the just-completed Birth Defects Study. The Agent Orange and the Vietnam Experience Studies have good potential for studying other adverse reproductive outcomes, such as infertility and miscarriages.

In your letter, you specifically asked about a proposed study at the National Institute for Occupational Safety and Health (NIOSH) addressing the issue of dioxin exposure and the production of birth defects. NIOSH has submitted for review to the AOWG Science Panel a proposed study of morbidity among workers in two plants that are listed in the NIOSH Dioxin Registry. This morbidity study has a reproductive component; however, the study is not a definitive examination of dioxin and birth defects. In the reproductive component, there is sufficient power to detect differences in fertility and miscarriages between individuals at these two plants and controls.

In addition to this proposed study, the investigators at NIOSH are attempting to determine whether the entire Registry contains adequate information to conduct a more rigorous study of birth defects among this dioxin-exposed worker population. Nevertheless, it is likely that if a study of the entire Dioxin Registry were to take place, it might have lower sensitivity to detect serious birth defects than the recently completed CDC Birth Defects Study . Following a preliminary assessment, NIOSH will be reporting back to the AOWG on the feasibility of a registry-wide study of reproductive effects. We will keep you informed of the progress of this assessment.

A final question in your letter addressed the views of the AOWG on what steps the Federal Government might take to assist Vietnam veterans who have children with birth defects or who are concerned about producing children with birth defects. Many steps have already been taken to respond to veterans' concerns. For example, the investigators from the CDC Birth Defects Study met with leaders of veterans' organizations, the news media, and many others to communicate the results of the Birth Defects Study. The study results also will be highlighted in videotape programs planned by the Veterans Administration (VA).

Though current evidence does not indicate that Vietnam veterans are at greater risk of fathering children with birth defects, birth defects in children of veterans and non-veterans alike are relatively common events. The VA has informed me that it has taken a number of steps to assist its environmental physicians, who conduct the Agent Orange Registry examinations nationwide, in responding to concerns raised by Vietnam veterans about birth defects.

While the VA does not have the authority to treat or examine the children of veterans except under certain rare circumstances, the VA can refer concerned veterans for genetic counseling. The VA has provided its environmental physicians with publications from the March of Dimes Birth Defects Foundation to assist in such referrals. The VA is also in the process of publishing a monograph on birth defects and genetic counseling. In the meantime, the VA has distributed to its medical centers a book, Clinical Genetics and Genetic Counseling, by Dr. Thaddeus E. Kelly. The VA published literature reviews also contain information about the relationship between Agent Orange exposure and birth defects.

Should you wish further information, I am ready to provide it.

Sincerely yours,

Edward N. Brandt, Jr., M.D.
Chair pro tempore, Cabinet Council
Agent Orange Working Group

Enclosures

cc:
The Honorable Harry N. Walters

JAMA
THE JOURNAL of the
American Medical Association
August 17, 1984 Vol 252, No 7

Original Contributions

Vietnam Veterans' Risks for Fathering Babies With Birth Defects

J. David Erickson, DDS, PhD; Joseph Mulinare, MD, MSPH; Philip W. McClain, MS; Terry G. Fitch, MA; Levy M. James, MS; Anne B. McClearn; Myron J. Adams, Jr, MD

• Vietnam veterans' risks for fathering babies with major structural birth defects were assessed using a case-control study. Information regarding military service in Vietnam was obtained from interviews with mothers and fathers of babies in case and control groups and from review of military records. Vietnam veterans, in general, did not have an increased risk of fathering babies with defects (all types combined; relative risk estimate, 0.97). Vietnam veterans who had greater estimated opportunities for Agent Orange exposure did not seem to be at greater risk for fathering babies with all types of defects combined. However, for a few specific types of defects the estimated risks were higher for subgroups of Vietnam veterans that may have had a greater likelihood of exposure to Agent Orange. These seemingly higher risks could be chance events, the result of some experience in the Vietnam service of the father, or the result of some other unidentified risk factor.

(*JAMA* 1984;252:903-912)

THIS REPORT describes the results of a case-control study designed to determine if men who served in the US military in Vietnam have been at increased risk of fathering babies with serious congenital malformations. This study was conducted primarily because of the concern expressed by many Vietnam veterans that they may have suffered from a variety of ailments as a consequence of their service there. The possibility of increased risks for fathering babies born with birth defects has been among the foremost of their concerns. A few anecdotes related to this specific concern have appeared in the correspondence sections of some medical journals,[1,2] but until recently there have not been any published reports of studies of humans specifically conducted to address this concern.[3]

Many Vietnam veterans are particularly concerned that their problems (or their alleged increased risk for problems) stem from exposure to herbicides in Vietnam, particularly the herbicide known as "Agent Orange." Agent Orange was an equal mixture of two herbicides, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid.[4] The compound 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) was a synthetic contaminant of the 2,4,5-trichlorophenoxyacetic acid. Much of the herbicide used in Vietnam was dispersed by the Ranch Hand Program from fixed-wing aircraft, but other methods of application were also used.

It is well known that the exposure of pregnant women to certain chemicals can result in disturbed embryogensis and consequent birth defects. The potential for paternally derived birth defects as a result of chemical exposures is, however, largely unknown. Based on current understanding of human reproduction, Friedman[5] suggests that such exposures in fathers could cause birth defects in three ways: (1) by gene mutation, (2) by chromosomal mutation, or (3) by acting as a teratogen carried in the semen. The potential for Agent Orange or TCDD causing birth defects by one or more of these mechanisms is unknown.

Despite the special concern with herbicide exposure, however, this study was designed primarily to determine if Vietnam veterans (in general) have been at increased risk. This approach was taken because at the time the study was designed it did not seem to be possible to obtain any measure of herbicide exposure except by questioning individual Vietnam veterans.

METHODS

Selection of Cases and Controls

This study was based on the experiences of parents of selected babies born in the metropolitan Atlanta area during the years 1968 through 1980; these babies are referred to as "index" babies because it was through them that the study parents

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From the Center for Environmental Health, Centers for Disease Control, Atlanta.

Reprint requests to Birth Defects Branch, Chronic Diseases Division, Center for Environmental Health, Centers for Disease Control, Atlanta, GA 30333 (Dr Erickson).

were identified. The index babies in the case group were those (live born or stillborn) with serious structural congenital malformations (birth defects) and registered by the Metropolitan Atlanta Congenital Defects Program (MACDP) (the MACDP does not register other adverse reproductive outcomes such as infertility, spontaneous abortion, and physical or mental deficits that only become apparent later in childhood). This program attempts to ascertain all babies with defects diagnosed during the first year of life born to mothers resident in the area.[8] In all, about 13,000 babies with birth defects born during the years 1968 through 1980 were registered by the MACDP. Many of these babies had abnormalities usually classed as minor anomalies (eg, ear tags, hydrocele, or some forms of polydactyly). In order that this study be completed as quickly as possible, the babies in the case group were chosen only from among those who had defects coded by *International Classification of Disease*, eighth revision *(ICD-8)*,[9] rubrics that usually signify serious or major birth defects. A serious defect was defined as one that could be associated with premature death, cause substantial handicap, or require surgery or extensive medical care. This selection process resulted in the initial choice of 7,529 babies in the case group from among the 13,000 registered. The final number eligible for the study was 7,133 (Table 1). This reduction occurred for various reasons, including the exclusion of babies thought to have been given up for adoption, the random choice of one baby from families with more than one registered baby, and the selection of babies for a pilot study.

The index babies in the control group were selected from among the 223,421 babies who were live born in the Atlanta area during the years 1968 through 1980. These babies were selected with the aid of the State of Georgia Vital Records Unit. The babies were chosen so that they were approximately frequency matched to the babies in the case group with respect to the following characteristics (sampling design variables): race (white and other), year of birth, and hospital of birth (20 hospitals). Some of the babies thus chosen were index babies from the case group, and these were deleted from the control group (and retained in the case group).

The power (ie, ability) of a study to detect increased risks for fathering babies with defects depends on the magnitude of the true risk, the number of cases available, the number of controls available, the rate of the exposure of interest in the control group, and the level of significance chosen. The frequency of the major "exposure" variable of interest—the proportion of Vietnam veterans among the fathers of babies born without defects—was not known at the time the study was designed, but estimated to be 10% to 20%, based on information provided by the Atlanta office of the Veterans Administration. Estimations of statistical power based on the number of babies in the case group available from the registry and on the estimates of the frequency of Vietnam veteran fathers showed that little was to be gained by including more than about 3,000 babies in the control group. For this number of controls, coupled with the number of available babies in the case group, the power would be about 70% to detect an odds ratio (OR) of 1.2 for all types of birth defects combined and almost 100% to detect ORs of 1.5 or greater (two-tailed χ^2 test for 2 by 2 tables; $\alpha=0.05$). Adding more controls would not increase the power for detecting increases or decreases for all types of defects combined commensurate with the increased study time or expenditure required to include them. Moreover, the power to detect increased or decreased risks for specific types of defects was expected to be low, except for rather large relative risks (eg, 3.0). In such instances, the addition of controls above 3,000 would result in almost no gain in power. After a pilot study provided an estimate of participation rates (70%), 4,246 families in the control group were selected as being eligible for the study (Table 1).

Table 1.—Number of Interviews, by Case-Control Status, Race, and Parent Completing Interview

Race	Families Eligible	Parent Completing Interview*		
		Mother, No. (%)	Father, No. (%)	Mother and Father, No. (%)
White				
Case group	5,136	3,813 (74)	3,384 (66)	3,202 (62)
Control group	3,046	2,301 (76)	2,006 (66)	1,907 (63)
Total	8,182	6,114 (75)	5,390 (66)	5,109 (62)
Other				
Case group	1,997	1,116 (56)	593 (30)	537 (27)
Control group	1,200	728 (61)	420 (35)	372 (31)
Total	3,197	1,844 (58)	1,013 (32)	909 (28)
Total				
Case group	7,133	4,929 (69)	3,977 (56)	3,739 (52)
Control group	4,246	3,029 (71)	2,426 (57)	2,279 (54)
Total	11,379	7,958 (70)	6,403 (56)	6,018 (53)

*Figures in parentheses are numbers of parents interviewed as percentages of numbers of parents eligible for interview.

Study Data

Information about the families of babies in the case and control groups was gathered during interviews with the babies' mothers and fathers during the years 1982 and 1983; interviews were done using a computer-assisted telephone interviewing system. Before the parents could be interviewed, they had to be located. This location process began with information that was recorded, at the time of the babies' birth, on birth certificates or MACDP records. With the exception of names, much of the available information (eg, addresses) was not current when the study was done. As a result, locating parents was difficult and required the use of various locating sources. Care was taken to ensure that the information used could be applied equally to families in the case and control groups, and that the tracing staff should not be aware of the case or control status of the families. When parents were contacted, they were asked to participate in a study designed to help learn about the causes of birth defects—no specific mention was made of Agent Orange or service in Vietnam.

Each mother and father who was willing to participate was interviewed by two interviewers. The first interviewer for each parent asked about the parent's reproductive history. Because such history would include a description of the health of the index baby, the first interviewer could usually not avoid knowing whether the index baby belonged to the case or control group. Then, so that interviewer bias might be avoided, a second interviewer for each parent asked questions about a wide variety of exposures (eg, occupations, chronic diseases, and drugs; questionnaires are reproduced in a report by Erickson et al[7]) and had no opportunity to know the case- or control-group status of the index baby. In all, four different interviewers had contact with a family if both the mother and the father completed interviews.

Special emphasis was given to obtaining a history of paternal military service. For this study, a veteran was defined as a father who had served in the US military at any time in his life, and a Vietnam veteran was defined as a father who had served in Vietnam in the US military before the conception of his index baby.

Each Vietnam veteran was asked if he believed he had been exposed to Agent Orange.

The Army Agent Orange Task Force also gave most Vietnam veterans a graded score reflecting their estimated opportunities for exposure to Agent Orange. The Exposure Opportunity Index (EOI) score was the result of a generally subjective evaluation made by a panel of service specialists on the basis of a veteran's occupation, location, and time of service in Vietnam; these specialists were familiar with the existing records of herbicide applications (records that document the time, place, and amount of herbicide used) and took them into account in the scoring process.

Some occupational and service groups were thought to have had more opportunities for exposure than others. For example, ground troops were much more likely to have had opportunities for exposure than, for example, shipboard personnel. In addition, veterans of the same branch of service with similar occupational specialities might have had different opportunities for exposure, depending on when and where they served in Vietnam. Most of the EOI scoring done for Vietnam veterans in this study required specific, detailed review and discussion of the particular circumstances; some examples can be found in the comprehensive report on this study.[8]

The EOI evaluations were done without knowledge of case or control status. Two separate EOI scorings were done—one based on occupation, location, and time recorded in military records, and the other based on similar information obtained from Vietnam veterans during the interviews.

The accuracy of Vietnam veterans' self-reports of Agent Orange exposure is unknown, as is the accuracy of the EOI, and it is unlikely that any validation will ever be possible. The records of troop movements and herbicide use that are available today were made for military purposes and not for the purpose of estimating exposure for epidemiologic studies. Nevertheless, at the time this study was designed, it was not thought possible to obtain any measure of Agent Orange exposure except by questioning Vietnam veterans themselves.

Analytic Approach

The birth defects that affected the index babies in the case group were categorized into 96 groups for the purpose of analysis. Some of the 96 groups were specified by individual *ICD-8* codes and others by various combinations of codes, including one group comprising all case babies (ie, all types of defects combined). A baby with more than one defect contributed one observation to each relevant-defect group. A special group consisting of babies whose defects were probably caused by a fresh dominant mutation was also formed.

Within each of the 96 defect groups four hypotheses were tested:

1. Veteran Status.—This was an evaluation of whether the risks of veterans for fathering babies with birth defects were different from those of nonveterans. The primary purpose of testing this hypothesis was to evaluate the possibility of a "healthy soldier" effect, although the possibility of increased risks was also entertained. Studies have shown that veterans tend to be healthier than their nonveteran counterparts.[9] This better health may or may not extend to reproductive health; no studies on the subject have been done. Testing the hypothesis seemed worthwhile because Vietnam veterans could possibly be at increased risk relative to other veterans but at decreased risk relative to nonveterans. For each defect group, if the test statistic for the hypothesis was significant ($P<.05$), and the OR estimate of the relative risk was less than 0.83 (or greater than its reciprocal, 1.20), the data for the tests of the remaining three hypotheses were limited to veterans.

2. Vietnam Veteran Status.—The evaluation of the hypothesis that the risk of Vietnam veterans was different from that of other men was the primary purpose of this study.

3. Agent Orange Exposure Opportunity Index.—The assessment of the possibility that the risk of fathering a baby with a defect was related to the EOI scores was assessed twice, once by using the EOI based on information derived from military records, and once by using the EOI derived from information provided by Vietnam veterans during the interviews.

4. Self-reports of Agent Orange Exposure.—The frequency of self-reported Agent Orange exposure was evaluated. Many persons will question the ability of Vietnam veterans to give accurate answers to the question of Agent Orange exposure, believing that there is a substantial possibility for response bias connected with case-control status. In other words, it is possible that men who have fathered babies born with defects may have searched their memories for possible causes of those defects. Differential reporting would result in biased estimates of risk. To reduce the possibility of such bias, the protocol for this study called for evaluating this hypothesis by comparing data on one type of defect with data on all other types of defects. This approach requires the assumption that the exposure of interest does not cause an increase in all or most types of defects.

Each of the hypotheses for each defect group was evaluated three times; each of the three evaluations was done with the data stratified on the sampling design variables (the variable, year of birth, was combined into three 52-month periods). First, risk estimates were made without consideration of potentially confounding variables (except for the sampling design variables). Second, risk estimates were made in which consideration was given to four covariables identified (before data analysis) by a group of specialists in birth defects as being particularly important. These four covariables were maternal age, maternal education, maternal alcohol consumption, and the occurrence of birth defects in first-degree relatives of the index babies. And third, consideration was given to 108 covariables.

The major analytical tool for the tests of hypotheses was conditional logistic regression.[10] A positive regression coefficient implies increasing risk and a negative coefficient implies decreasing risk. In addition, a logistic regression coefficient can be transformed into ORs, and an OR can be used as an estimate of relative risk. A relative risk is the ratio of two risks. For example, if Vietnam veterans had twice the risk of having babies with birth defects relative to other men, their relative risk would be 2.0. Likewise, if Vietnam veterans' risk was half that of other men, their relative risk would be 0.5.

Different subsets of the complete data were used for the various tests of hypotheses. For the analyses done without consideration of potentially confounding variables (except the sampling design variables), the following subsets were used: (1) Data taken from mothers' interviews were used for the Veteran Status and Vietnam Veteran Status hypotheses. This was done because more mothers than fathers were interviewed, and because mothers' answers were shown to agree closely with fathers' answers (where both mother and father were interviewed) to the questions regarding the fathers' veteran and Vietnam veteran status[8]; and (2) all fathers' interviews were used for the hypotheses concerning Agent Orange exposure because mothers were not good substitutes for fathers insofar as this issue was concerned and, furthermore, because they were not fully questioned about the issue. For the analyses that took account of potentially confounding variables, the data were (for the most part) derived from mothers' and fathers' interviews from families in which both the mother and father completed interviews.[8]

Three supplementary issues related to military service in Vietnam were also evaluated:

1. Vietnam Veteran Birth Defect Syndrome.—The data were analyzed to see if the fathers of babies with particular combinations of defects were more frequently

Vietnam veterans than were the fathers of index babies in the control group. Combinations of pairs and triplets of *ICD-8* defect codes were evaluated. For example, the frequency of Vietnam veterans among the fathers of babies with the defect-pair anencephalus and omphalocele was compared with the frequency among the fathers of index babies in the control group.

2. Vietnam Veterans' Risks for Fathering Several Affected Babies.—The possibility that Vietnam veterans have had a persistent increased risk of fathering more than one baby with birth defects was evaluated within the case group as follows: the frequency of defects in siblings born after the index babies of Vietnam veteran fathers was contrasted to the frequency in later-born siblings of index babies whose fathers did not serve in Vietnam.

3. Malaria and Malaria Chemoprophylaxis.—Each interviewed Vietnam veteran father was asked if he had contracted malaria while he was in Vietnam; each was also asked if he had taken medicines for preventing malaria. This was the only health-related issue about which Vietnam veterans received special questioning—there were no queries about other diseases that men may have contracted in Vietnam. The controls for the fathers of babies with a particular type of defect were the fathers of babies with all other types of defects (this was done for the same reason as mentioned herein in reference to the use of the technique for evaluating self-perceived Agent Orange exposure).

RESULTS

Overall, 69.9% of eligible mothers and 56.3% of eligible fathers completed interviews (Table 1), and an additional 1% or so of mothers and fathers partially completed interviews to the point that a paternal military history was obtained.[6] The participation rate for parents of the white race was substantially higher than that for parents of other races, particularly for fathers (Table 1). No notable differences in the case-control participation rates were noted for white parents, but for parents of other races the control-group participation rates were about 5% higher than those for the case group (Table 1). This difference was shown to be of little concern insofar as it might affect the inferences to be drawn regarding the risks of Vietnam veterans.[6] With stratification on race, there was equal participation of families in the case and control groups with respect to the other sampling design variables: year of birth and hospital of birth. In addition, there was relatively little variation in the participation rates for families in the case group associated with the type of defects that affected the index babies.

Roughly 50% of the fathers of white index babies were said by the mothers to have served in the military, in contrast to about 30% of fathers of other race index babies. About 9% to 10% of fathers of white index babies were said by mothers to be Vietnam veterans as compared with 6% to 7% of fathers of other race index babies; again, there was not much difference in the case- and control-group rates. As stated by mothers, about 2% of white fathers could not be classified as to whether they were Vietnam veterans as compared with 6% to 7% of other race fathers. Slightly more than 10% of interviewed white fathers said that they were Vietnam veterans, and the percentage for interviewed other race fathers was about the same. The fact that there was not a higher proportion of other race fathers who were Vietnam veterans, as compared with white fathers, may surprise some readers. It is popularly believed that a disproportionate number of black men served in Vietnam. We now know, however, that this was not the case, although those black men who did serve there may have borne a

Table 2.—Veterans' and Vietnam Veterans' Risks for Fathering Babies With Birth Defects*

Group	Risks for Veterans†		
	Veteran Fathers,‡ No. (%)	Nonveteran Fathers, No. (%)	Total, No. (%)
Case group	1,659 (38)	2,727 (62)	4,386§(100)
Control group	1,047 (39)	1,652 (61)	2,699 (100)
	Risks for Vietnam Veterans‖		
Group	**Vietnam Veteran Fathers, No. (%)**	**All Other Fathers, No. (%)**	**Total, No. (%)**
Case group	428 (9)	4,387§(91)	4,815 (100)
Control group	268 (9)	2,699 (91)	2,967 (100)

*All types of defects combined. Figures in parentheses are percentages of totals.

†Logistic regression odds ratio, 0.94. Odds ratio 95% confidence limits, 0.85 to 1.04.

‡Vietnam veteran fathers excluded from tabulation.

§The figures 4,386 and 4,387 are correct; added case in column 2, subheading "All Other Fathers," results from gain of stratum-matched Vietnam veteran control fathers.

‖Logistic regression odds ratio, 0.97. Odds ratio 95% confidence limits, 0.83 to 1.14.

Table 3.—Birth Defects Risks and Agent Orange Exposure Opportunity Indices*

Index	Index Score†	Case Group, No. (%)	Control Group, No. (%)
Index according to information obtained from military records‡	0	3,605 (92)	2,200 (93)
	1	121 (3)	73 (3)
	2	60 (2)	31 (1)
	3	54 (1)	34 (1)
	4	40 (1)	18 (<1)
	5	44 (1)	23 (1)
Total	...	3,924 (100)	2,379 (100)
Index according to information obtained during interview§	0	3,605 (91)	2,200 (92)
	1	118 (3)	78 (3)
	2	70 (2)	46 (2)
	3	79 (2)	41 (2)
	4	53 (1)	23 (1)
	5	26 (<1)	14 (<1)
Total	...	3,951 (100)	2,402 (100)

*Risks for fathering babies with all types of defects combined. Figures in parentheses are percentages of totals. Vietnam veteran fathers not classified because of insufficient information have been omitted.

†Index score of 0 given to all fathers who did not serve in Vietnam; scores of 1 to 5 reserved for Vietnam veterans. The odds ratio estimate of the relative risk at each exposure-opportunity index score level can be obtained by the relationship $OR_i = \exp(\text{coefficient} \times \text{score}_i)$.

‡Logistic regression coefficient, 0.03. Coefficient 95% confidence limits, −0.04 to 0.10.

§Logistic regression coefficient, 0.04. Coefficient 95% confidence limits, −0.03 to 0.11.

somewhat heavier burden of combat."

Estimations of the relative risks (OR estimates) for veterans and Vietnam veterans for fathering babies with all types of defects combined are presented in Table 2 (these analyses took account of the sampling design variables, but not of other potentially confounding variables). There were 1,659 fathers of babies in the case group and 1,047 fathers of babies in the control group who were veterans (excluding Vietnam veterans) and 2,727 fathers of babies in the case group and 1,652 fathers of babies in the control group who were not veterans. The OR (relative risk) as estimated by logistic regression using the maximum likelihood method is 0.94, with 95% confidence limits of 0.85 to 1.04. Thus, there is no evidence in favor of the position that veterans (excluding Vietnam veterans) have had a different risk for fathering babies with the aggregate of the birth defects studied here. Because there is no such evidence, the tests of the remaining hypotheses made comparisons of the frequency of Vietnam veterans (and subsets of them) with nonveterans as well as other veterans. The OR for Vietnam veterans fathering babies with defects is 0.97, not significantly different from 1.0 at the 95% confidence level (Table 2). Therefore, there is no support in these data for the proposition that Vietnam veterans (in general) have been at different risk than other men for fathering babies with the types of birth defects that we studied.

The distributions of Vietnam veterans on the two variants of the EOI are presented in Table 3 (a score of 1 indicated minimal opportunities for exposure; 5, the highest opportunities; and scores of 2, 3, and 4, graduated intermediate opportunities). Among those who were classified on both variants, 52% received the same score, and about 84% received the same score plus or minus 1. For each of the two EOI variants a logistic regression model was fitted. In both cases the resultant regression coefficients were not significantly different from 0 (Table 3), indicating no evidence for either an increase or a decrease in the risk for fathering babies with birth defects related to the EOI scores.

About 25% of interviewed Vietnam veterans believed that they had been exposed to Agent Orange, whereas roughly the same proportion said that they did not know if they had been exposed. For the defect group "All Case Babies," no tests of hypotheses regarding self-reported exposure to Agent Orange were done. As described previously, the frequency of self-reported exposure was assessed only among the fathers of babies in the case group, and as the name of the group "All Case Babies" implies, no control group was available. However, the tests were done for all other defect groups.

The tests of hypotheses for the remaining 95 defect groups are presented in an abbreviated form in Table 4. As an aid to the reader in interpreting Table 4, the results for the group "All Case Babies" presented in Tables 2 and 3 are repeated in Table 4. The OR estimates for the tests of hypotheses regarding risks associated with self-reported exposure to Agent Orange are also presented in Table 4; for example, for the defect group "Multiple Defects" the relative risk estimate was 1.07, not significantly different from 1.0 ($P > .05$).

For the most part, the tests of hypotheses for the remaining 95 defect groups (Table 4) yielded results similar to those just described. Some important departures from the general finding of no different risks for Vietnam veterans (and subsets of them) will be described. Some statistically significant findings are not described but can be identified in Table 4, and still others can be found in the comprehensive report on this study.[3]

The estimated risks for fathering babies with spina bifida are higher for Vietnam veterans with the higher EOI scores. The 20 Vietnam veteran fathers of babies with spina bifida who received scores on the EOI derived from information contained in military records were distributed as follows: score 1, five fathers; score 2, four fathers; score 3, six fathers; score 4, three fathers; and score 5, two fathers. The distribution of Vietnam veteran fathers' scores on the interview-derived EOI was 3, 2, 6, 7, and 1 for scores of 1 through 5, respectively. The regression coefficient for the first EOI implies ORs of 1.2, 1.4, 1.6, 1.9, and 2.2 for scores of 1 through 5, respectively, and the coefficient for the second EOI implies ORs of 1.2, 1.5, 1.8, 2.2, and 2.7.

Veterans had a higher estimated risk for fathering babies with cleft lip with or without cleft palate, as did Vietnam veterans who had higher scores on the second EOI; the distribution of Vietnam veteran fathers was 3, 7, 1, 4, and 5 for scores of 1 through 5, respectively. The regression coefficient implies ORs of 1.2, 1.4, 1.6, 1.9, and 2.2 for scores of 1 through 5, respectively.

Vietnam veterans with higher scores on the second EOI had higher estimated risks for fathering babies with "Other Neoplasms"; the distribution of fathers was 4, 4, 3, 2, 0 for scores of 1 through 5, respectively. The coefficient implies ORs of 1.3, 1.7, 2.2, 2.8, and 3.7. The estimated risk for the Vietnam veteran hypothesis had 95% confidence limits of .99 to 3.29. The neoplasms classified in this group include (for Vietnam veteran and all other fathers) dermoid and epidermoid cysts (26 cases), teratomas (14 cases), lipomas (nine cases), hamartomas (five cases), CNS tumors (five cases), Wilms' tumors (three cases), neuroblastomas (three cases), hepatoblastoma (one case), rhabdomyosarcoma (one case), and miscellaneous benign tumors (24 cases).

The analyses in which the potential confounding effects of covariables were evaluated gave results very similar to those just presented, indicating that the covariables were not important confounding variables in this study. The only substantial departure from this general picture was that Vietnam veterans had significantly lower estimated risks for fathering babies with defects classed in the group "Complex Cardiovascular Defects" when consideration was given to those covariables identified as being particularly important before analysis (OR, 0.59).

In seven families in the case group the father stated that he had been exposed to Agent Orange and the mother reported birth defect-affected siblings born after the index baby; this was a significantly higher number than expected on the basis of the frequency in other families in the case group (OR, 2.57). No striking

Table 4.—Tests of Hypotheses for Birth Defects Risks*

		Hypotheses†				
					Agent Orange Exposure Opportunity Indices, Regression Coefficients	
Defect Group	No. of Cases‡	Veteran, Odds Ratio	Vietnam Veteran, Odds Ratio	Self-report Agent Orange Exposure, Odds Ratio	1	2
All case babies	4,815	0.94	0.97	. . .	0.03	0.04
Multiple defects	1,137	0.93	0.99	1.07	0.03	0.06
Total nervous system defects	663	0.96	0.91	0.78	0.06	0.07
Total eye defects	113	0.71	0.91	0.42	−0.00	−0.02
Total cardiovascular defects	1,012	0.91	0.92	0.97	0.01	0.02
Complex cardiovascular defects	443	0.97	0.89	0.65	−0.07	−0.11
Total respiratory tract defects	35	1.00	0.87	1.08	−0.23	0.05
Total gastrointestinal tract defects	1,008	1.07	0.96	1.09	0.02	0.06
Total sex organ defects	267	0.81	0.92	1.16	0.09	0.02
Total urinary tract defects	214	1.06	0.93	0.81	−0.06	−0.06
Total musculoskeletal defects	1,014	0.90	0.96	1.06	0.01	0.00
Total endocrine defects	44	1.10	0.86	. . .	−0.13	0.01
Autosomal chromosome defects	257	1.29	0.81	0.75	−0.13	−0.17
Dominant mutations	19	0.62	. . .	. . .	. . .	. . .
Anencephalus and spina bifida	343	1.13	0.90	1.03	0.06	0.11
Anencephalus	142	0.90	0.89	0.80	−0.07	−0.10
Spina bifida	201	1.25	1.05	1.19	0.16	0.20
Hydrocephalus	68	0.65	0.86	0.25	0.04	0.04
Encephalocele	30	0.59	1.21	. . .	0.19	0.15
Microcephalus	86	1.07	1.14	2.15	0.16	0.16
Neurofibromatosis	6	0.56	. . .	. . .	. . .	. . .
Anophthalmia	8	0.16	2.65	. . .	. . .	. . .
Microphthalmos	44	1.06	0.76	. . .	−0.47	−0.12
Buphthalmos	6	1.86	1.80	. . .	. . .	. . .
Congenital cataract	42	0.79	1.20	. . .	0.11	−0.21
Coloboma	16	0.75	1.36	3.45	0.24	0.42
Aniridia	3	0.45	. . .	. . .	. . .	. . .
Anomalies of ear causing impaired hearing	81	1.40	1.24	. . .	−0.70	−0.81
Conus arteriosus defects	155	0.79	0.81	1.06	−0.10	−0.01
Common truncus	24	0.89	0.67	. . .	0.10	0.22
Transposition great vessels	91	0.88	0.75	1.49	−0.36	0.07
Tetralogy of Fallot	65	0.89	0.79	0.81	0.02	−1.02
Ventricular septal defect	404	0.87	1.00	1.01	0.06	0.03
Selected ventricular septal defects	322	0.95	0.97	0.98	0.02	−0.07
Atrial septal defect	176	0.82	0.84	0.24	0.05	0.04
Ostium atrioventriculare commune	35	0.87	0.66	0.89	−0.02	−0.01
Anomalies of heart valves	158	1.07	0.71	1.01	0.11	0.07
Fibroelastosis cordis	7	0.96	. . .	. . .	. . .	. . .
Patent ductus arteriosus	376	0.89	0.81	0.74	−0.11	−0.13
Selected patent ductus arteriosus	333	0.84	0.82	0.89	−0.14	−0.14
Coarctation of aorta	75	1.01	1.26	1.89	0.03	0.06
Other anomalies of aorta	63	1.25	0.60	. . .	−0.09	−0.06
Stenosis atresia of pulmonary artery	83	0.66	0.53	. . .	−0.07	−0.04
Anomalies of great veins	39	0.90	0.82	. . .	−0.06	0.11
Choanal atresia	24	1.04	0.77	1.41	−0.25	0.14
Congenital cystic lung	4	1.47	. . .	. . .	. . .	. . .
Agenesis of lung	7	0.62	1.86	. . .	−0.09	−0.03
Cleft palate	117	0.73	0.56	0.76	−0.47	−0.08
Cleft lip without cleft palate	131	1.40	1.10	1.07	0.06	0.18
Pyloric stenosis	317	1.15	0.90	0.80	0.00	0.00
Tracheoesophageal fistula, esophageal atresia, and stenosis	62	1.11	1.16	0.89	0.14	0.22

Table 4.—Tests of Hypotheses for Birth Defects Risks* (Cont)

		Hypotheses†				
					Agent Orange Exposure Opportunity Indices, Regression Coefficients	
Defect Group	No. of Cases‡	Veteran, Odds Ratio	Vietnam Veteran, Odds Ratio	Self-report Agent Orange Exposure, Odds Ratio	1	2
Atresia and stenosis of small intestine	74	0.77	0.81	0.71	−0.80	−0.27
Atresia and stenosis of rectum and anal canal	89	1.26	0.80	1.09	−0.00	−0.06
Hirschsprung's disease	39	0.77	1.12	2.43	0.09	−0.06
Anomalies of intestinal fixation	41	1.40	0.89	3.11	−0.17	0.22
Anomalies of gallbladder, bile ducts, and liver	20	0.51	2.06	1.91	0.18	−0.29
Anomalies of pancreas	8	0.49	. . .	. . .	. . .	. . .
Indeterminate sex	5	2.26	. . .	. . .	. . .	. . .
Hypospadias	383	0.83	0.76	0.86	0.03	−0.04
Epispadias	17	0.60	1.30	. . .	. . .	. . .
Anomalies of ovary, fallopian tubes, and uterus	18	0.83	0.83	2.18	0.08	−0.00
Anomalies of vagina and external female genitalia	40	0.92	1.10	0.94	0.13	−0.02
Pseudohermaphroditism	38	0.90	0.79	. . .	−0.07	0.09
Renal agenesis	80	1.11	0.71	. . .	−0.27	−1.00
Cystic kidney disease	60	0.78	0.53	. . .	−0.83	−0.52
Urinary tract obstructive defects	86	0.88	1.22	0.80	0.06	−0.06
Exstrophy of urinary bladder	9	2.88	1.42	. . .	−0.23	0.26
Atresia stenosis of urethra and bladder neck	49	1.42	0.96	. . .	−0.06	0.00
Clubfoot	849	0.90	1.02	1.19	−0.00	0.01
Selected clubfoot	547	0.88	0.99	1.26	−0.02	0.01
Reduction deformity	157	1.02	1.03	1.13	0.11	0.06
Generalized flexion contracture of limb joints	21	1.11	2.93	1.03	0.18	0.32
Chondrodystrophy	34	0.47	. . .	. . .	. . .	. . .
Osteogenesis imperfecta	7	0.89	. . .	. . .	. . .	. . .
Hereditary edema of the legs	3	. . .	. . .	. . .	. . .	. . .
Specified anomalies of hair	13	0.64	2.01	8.89	0.45	. . .
Specified anomalies of nails	16	2.14	4.22	. . .	0.93	0.46
Anomalies of spleen	41	1.22	0.56	. . .	0.04	−0.12
Anomalies of adrenal gland	6	0.75	. . .	. . .	. . .	. . .
Anomalies of thyroid gland	26	0.80	0.74	. . .	0.02	0.14
Anomalies of other endocrine glands	14	1.69	0.88	. . .	. . .	−0.27
Situs inversus	13	0.81	2.52	. . .	0.54	0.60
Conjoined twins	4	0.41	. . .	. . .	. . .	. . .
Other forms of monster	8	0.95	. . .	. . .	. . .	. . .
Down's syndrome	212	1.30	0.95	0.73	−0.06	−0.12
Other syndromes caused by autosomal abnormality	46	1.27	0.22	0.86	−0.81	−0.04
Tuberous sclerosis	1	. . .	. . .	. . .	. . .	. . .
Other specified syndromes	90	0.82	2.01	0.69	0.09	0.18
Potter's syndrome	49	0.86	0.63	. . .	−0.20	. . .
Multiple congenital anomalies, unspecified	3	2.76	. . .	. . .	. . .	. . .
Diaphragmatic hernia	74	1.41	0.89	0.47	−0.19	−0.84
Omphalocele and gastroschisis	108	0.84	1.41	1.51	0.16	0.15
Other neoplasms	87	0.85	1.80	1.80	0.14	0.29
Cytomegalovirus	10	1.67	1.25	. . .	. . .	. . .
Herpes simplex	10	1.84	4.22	. . .	0.18	0.81
Syphilis	7	0.57	. . .	. . .	. . .	. . .

*Significant odds ratios or regression coefficients ($P<.05$) are underlined. Ellipses indicate that test was not done because there were no exposed cases and/or exposed controls. "All case babies" test was not done because it was considered inappropriate (see text).

†Veteran hypothesis, estimated relative risk (odds ratio) for veteran fathers (excludes Vietnam veterans); if significant, and odds ratio was less than 0.83 or greater than 1.2, data for remaining hypotheses limited to families with veteran fathers. Vietnam veteran hypothesis, estimated relative risk (odds ratio) for Vietnam veteran fathers. Self-report Agent Orange exposure, estimated relative risk (odds ratio) for self-reported exposure to Agent Orange. Agent Orange exposure-opportunity indices, logistic regression coefficient for association between birth defects risk and index scores. Index 1 derived from information in military records. Index 2 based on information obtained from fathers' interviews.

‡Number of case-group families contributing to analysis of Vietnam veteran hypothesis.

"syndrome" of defects (based on combinations of *ICD-8* codes) was found among the babies in the case group born to Vietnam veterans.

Fathers of babies born with defects classified in the "Total Sex Organ Defects" group were more likely to have said that they had contracted malaria while they were in Vietnam than were the fathers of other babies in the case group (OR, 3.44; 95% confidence limits, 1.60-7.41; 11 out of 246 fathers of babies with sex organ defects reported malaria in contrast to 20 out of 1,537 fathers of babies with other defects). The results were very similar for the group "Hypospadias," which accounted for most of the babies classified in the former group. No associations were found between the occurrence of defects and reported use of antimalarials.

COMMENT

The most important conclusion to be drawn from this study is that the data collected contain no evidence to support the position that Vietnam veterans have had a greater risk than other men for fathering babies with all types of serious structural birth defects combined. Many fathers, whether Vietnam veterans or not, have had the misfortune of having babies with birth defects. Although specific types of structural birth defects are rare, when all types are combined they usually affect roughly 2% to 3% of stillborn and live-born babies. A large number of American men served in Vietnam—2.6 million as estimated by the Veterans Administration.[13] Because most of these men were quite young when they served, a large number of babies will have been born to them during the past 15 years or so. If these men have had an average of one baby each since the time of their service, they will have had 52,000 to 78,000 babies born with serious defects if they have had the usual risk of 2% to 3%. If these men have had an average of two babies each, then these figures would be doubled. Although these numbers may seem alarming, they are based on nothing more than assumptions about the fertility of Vietnam veterans and the usual rate at which birth defects occur.

This study cannot prove that some factor associated with service in Vietnam was or was not associated with the occurrence of rare types of defects, of defects in the babies of selected persons, or of defects in the babies of small groups of veterans. However, the conclusion that Vietnam veterans in general have not fathered babies with all types of birth defects combined, at higher rates than other men is based on relatively strong evidence. This study has not identified the causes of the birth defects that have occurred in the babies of Vietnam veterans, nor in the babies of men who did not serve in Vietnam. The causes of the vast majority of birth defects remain unknown. Two to three percent of the babies born to Vietnam veterans in the future will have serious birth defects, just as will a similar proportion of babies born to other men. The discovery of the causes of these defects, discovery that may make prevention possible in the future, will depend on other research.

In addition, this study does not provide support to the notion that those men who may have been exposed to Agent Orange in Vietnam have had an increased risk of fathering babies with most types of defects. The conclusion regarding the lack of increased risks associated with Agent Orange is based on considerably weaker evidence than the conclusion about Vietnam veterans in general.

Any study in which information is not obtained from all of the target sample engenders concern that persons who did not participate are different from those who did and that this difference might be a source of bias in the study results. The main reason for nonparticipation in this study was that parents could not be located. Participation rates for other race parents were lower than those for white parents, particularly for fathers. This fact may limit our ability to generalize the study results for other race fathers. However, assessments were made for the possibility that the risks for white and other race fathers varied (for each of the hypotheses for each of the defect groups), and few differences were found.

The data on some of the exposures of interest had to be collected from parents, not from some external source. In most case-control studies, there is fear that members of the case and control groups will not give exposure histories with equal accuracy, thereby introducing bias into the case-control comparisons. For the main exposure in this study, paternal military service in Vietnam, we believe that there is little reason for concern about the accuracy of information reported by either parents in the case or control group.

However, the ability of Vietnam veterans to give valid reports of exposure to Agent Orange is a matter for debate. In addition, some observers will also adhere to the position that only a small proportion of Vietnam veterans had a potential for exposure. Rather than enter these debates, the approach of this study was to listen to the reports of Vietnam veterans and to use comparison techniques that should reduce possible case-control response biases. About one fourth of Vietnam veterans who participated in this study believed that they had been exposed to Agent Orange. It is a strength of this study that their assessment of exposure was used in the analysis. The potential for bias in the analyses of the self-reports of Agent Orange exposure has presumably been reduced by using only the parents of babies born with defects as controls. However, the success of this technique cannot be fully known.

The validity of the Agent Orange EOI is uncertain and will probably remain so. The records that must be used today to make estimates of exposure possibilities were made for military purposes, not for the purpose of conducting health studies. However, the index scoring for this study was done by service personnel familiar with the existing records that document the use of herbicides in Vietnam by time and place. This staff also had personnel files at hand from which to document Vietnam veterans' occupations and military units and records from which to estimate the locations of the units at various times. Moreover, a separate index scoring was done for which information on location and occupation was obtained from the men during the interviews. Again, use was made of information given by veterans, and this is considered a strength of the study. Finally, the scoring was done by service staff who had no knowledge of the case- or control-group status of the individual veterans; therefore, there can be no question about scoring biases being connected with case-control status, as there is in respect to the self-reports of Agent Orange exposure.

Although the overall results of this study indicate that Vietnam veterans (and subsets of them described by their potential exposure to Agent Orange) are not at increased risk for fathering babies with the aggregate of all the types of birth defects studied here, we found some statistically significant results; however, they may not be biologically significant. In considering these findings, it must be kept in mind that many hypotheses were tested in this study, and some statistically significant differences were to be expected, even if no true differences in risk exist in the populations from which the parents in case and control groups were drawn. A statistically significant result does not necessarily mean that there are true differences in risk. One can only say, on the basis of the associated probability level, a particular finding would arise only infrequently because of chance vagaries of the sampling process. In this circumstance, it seems appropriate to discuss these findings in the context of the several factors that need to be considered in the inferential process. Alternatively, it must be kept in mind that this study had only a low power to detect modestly increased risks for individual types of defects that have affected small numbers of babies.

An association between spina bifida and the two Agent Orange EOIs is noted—there seem to be increasing risks with increasing scores on the indices. While there are some differences in the epidemiology and embryology of anencephalus and spina bifida, they are generally thought to be etiologically related defects.[13] Although the logistic regression coefficients for the indices for anencephalus are not significant, the point estimates are negative, suggesting a lower risk for those men who had the higher index scores. Therefore, the lack of an association between the indices and anencephalus suggests that the associations with spina bifida may be chance phenomena.

Vietnam veterans' risk for fathering babies with congenital neoplasms was 1.8 (Table 4), with 95% confidence limits of 0.99 to 3.29. The regression coefficient associated with the Agent Orange EOI based on interviews was significantly greater than 0.0. The point estimates of the risks found here are rather low, of such a level that they could conceivably be the result of some unknown bias or unmeasured confounding factor. They could be chance events, or they could be the result of some experience in the Vietnam service of fathers. The same may be said for the positive associations noted for cleft lip with or without cleft palate (Table 4).

Vietnam veterans (in general) do not seem to have had a greater than normal risk of fathering more than one baby with birth defects. However, a significantly higher proportion of men who believed that they had been exposed to Agent Orange had a second affected baby (born after the affected index baby) than did other fathers of babies in the case group who believed that they had not been exposed or who were not Vietnam veterans. Because the control group was expected and found to have fewer families with affected babies born after the index baby than there were among the families in the case group, they were not used as a point of reference. Instead, the comparisons were done with families in the case group in which the fathers were not Vietnam veterans or were Vietnam veterans who said that they were not exposed to Agent Orange. This approach is similar to the approach taken for the other analyses of the self-reports of Agent Orange exposure, an approach that was taken for the purpose of reducing possible case-control bias. Conceivably, this association is an expression of a case-control bias in which fathers with only one affected baby were less likely to report self-perceived exposure.

The apparent association between malaria and hypospadias is of interest. Malaria infection was a major disease problem for military medicine in Vietnam.[14] Vietnam veterans' reports of malaria were not validated, as for example by review of medical records, but their statements about treatment received lend credence to their reports of malaria.

How do the results of this study compare with the results of related studies? The most directly comparable is the study of birth defects risks among Australian Vietnam veterans, conducted by the Commonwealth Institute of Health.[7] It showed, in a matched-pair design of 8,517 cases and controls, no increased risk of all types of structural birth defects combined among men who served in Vietnam in the Australian Army. Kunstadter[15] reviewed Vietnamese hospital records from 1962 through 1973 and found no increased frequencies of defects in babies born to mothers possibly exposed to herbicides; his study was not designed to show the possible effects of exposure of fathers. Tung et al[16] reported histories of the families of North Vietnamese veterans who had served in sprayed areas of the South. He presented several case reports of children with birth defects whose parents stated that they were sprayed with herbicides. The description provided no opportunity for comparison with families exposed to herbicide who did not have children with birth defects.

In several other studies, male and female exposures outside of Vietnam have been evaluated,[17-21] but no adverse human reproductive effects have been conclusively demonstrated to be related to exposure to pheonoxy herbicides and dioxin. Evidence and concern for such ill effects come from experiments in which laboratory animals are used. These adverse outcomes occur after chemicals are administered to pregnant females at critical times during gestation.[22] Animal experiments in which paternal exposures have been evaluated have had negative results.[23]

The pattern just described is not unusual. The ability of drugs and infections to cause reproductive problems by maternal-fetal exposures is well known (eg, thalidomide and rubella). Conversely, there have been no unequivocal demonstrations of such effects acting through paternal exposures.[24] The risks for fathering babies with defect syndromes caused by fresh dominant mutations (eg, achondroplasia) is known to increase with increasing paternal age.[25] This association was the basis for forming, for this study, a special group of babies born with defects thought likely to be caused by fresh dominant mutations. It is now known that about 25% of babies born with trisomy 21 (Down's syndrome) derive their extra chromosomes from their fathers.[26] Whether the paternal-age associations with dominant mutations or the paternal contributions of extra chromosomes in Down's syndrome are caused by environmental exposures is unknown. Indeed, the possibility of more general paternal contributions to the occurrence of birth defects has not been extensively investigated.

The studies of human populations with well-documented exposure to herbicides and/or dioxin have been small. Such small studies have only a weak ability to demonstrate even modestly increased risks; therefore, the fact that no increased risks have been demonstrated may reflect the weaknesses of the studies rather than a true lack of effect. Although the present study was large, the estimates of Agent Orange exposure that had to be used were probably rather inaccurate. Therefore, the conclusions regarding possible Agent Orange-associated risks for Vietnam veterans that can be drawn from this study are weak. Even so, this study provides strong evidence that Vietnam veterans in general are not at increased risk. This suggests that if there is any increased risk related to exposure to Agent Orange, either the risk must be small, must be limited to select groups of Vietnam veterans, or the increased risk must be limited to specific types of defects.

A more comprehensive report on this study has been published by the Centers for Disease Control. Copies can be obtained on request from the authors (reference 8).

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editorial

Vietnam and Birth Defects

Between 1962 and 1971, US military forces sprayed herbicides over 3.5 million acres of jungle in Vietnam.[1] The herbicides were identified by the color bandings on their containers (green, orange, purple, white, pink, and blue). They were used for defoliation, crop destruction, and to clear vegetation around military installations. The designation "Operation Ranch Hand" was used for the aerial dispersal of these herbicides from fixed-wing aircraft. Small quantities also were sprayed from helicopters and riverboats and by hand-held applicators. Agent Orange was the most widely used of these herbicides; more than 100 million pounds of the substance was sprayed in Vietnam during a ten-year period.[1]

Agent Orange is a 50:50 mixture of the butyl esters of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Both 2,4-D and 2,4,5-T have been used extensively in the United States for more than 30 years as agricultural herbicides in the control of broadleaf plants and to clear unwanted vegetation along rights-of-way.

Unfortunately, during its chemical synthesis, 2,4,5-T is contaminated by an unwanted by-product, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Although TCDD is only one of 75 chlorodioxins, this chloroisomer is considered to be the most toxic. When administered orally to different animal species, TCDD's median lethal dose varies from 1 μg/kg to 5 mg/kg.[2]

The 50,000 tons of Agent Orange used in Vietnam contained a total of 368 lb of TCDD, but almost 40% of the TCDD used in Vietnam was sprayed (in Agents Green, Pink, and Purple) before 1964, when there were few American troops in the field.[3] In addition to the TCDD-containing agents, 5 million gallons of Herbicide White (active ingredient, picloram) were dispersed. Picloram is highly carcinogenic in rodents and persistent in the environment. To add to the confusion, the military also sprayed malathion, a commonly used garden insecticide, near US military installations to kill mosquitoes and other insects. Thus, it is possible that many servicemen who were sprayed only with insecticides may believe they had come into contact with the herbicide Agent Orange.

Some 2.6 million Americans served in Vietnam. This includes 1,200 crewmen in Operation Ranch Hand, and some 200 civilians who were involved in the "dedrumming" and destruction of 2.2 million gallons of surplus Agent Orange. A number of men who served in Vietnam have complained of various medical conditions including weight loss, liver damage, skin diseases, and birth defects in their offspring, which they related to their exposure to Agent Orange. These complaints led to class action suits filed against several herbicide manufacturers, the Veterans Administration, and the Department of Defense.

Information on the hazards of TCDD to humans comes from studying the few industrial accidents where known exposure has occurred. The most striking abnormality associated with contact with TCDD is the development of chloracne. This acneiform disorder was first described by Herxheimer in 1899 and was noted to be associated with contact with chlorinated hydrocarbons in 1918. It is now believed to be one of the most common forms of occupational dermatitis. In 1949, more than 200 men were exposed to TCDD when a runaway chemical reaction occurred in the manufacture of 2,4,5-T in Nitro, WVa.[4] Chloracne developed in more than 85% of the exposed persons. When examined 30 years after the accident, more than half of those exposed had persistent chloracne, but no increased mortality or increased risk of heart disease or hepatic or renal damage was noted. The most extensively investigated accident involving TCDD occurred in Seveso, Italy, in 1976.[5] A ruptured chemical-reaction vessel released a cloud of TCDD over a 6-square mile area and potentially exposed more than 36,000 people to varying concentrations of the dioxin. The primary clinical finding was chloracne in the most exposed group, although evidence of transient nervous system and hepatic effects were seen. There was no substantial change in the observed rates of spontaneous abortions or birth defects. Although none of the people exposed to TCDD died, thousands of herbivorous animals did. When administered orally, TCDD is highly toxic, and observations at Seveso and other sites of industrial accidents suggest that ingestion is necessary for the development of its full toxicity. These accidents also provide evidence that chloracne is the best indicator of significant human exposure.

Despite the lack of evidence of increased incidence of congenital malformations in children of parents exposed to large doses of TCDD, there has still been concern that birth defects observed in children of men serving in Vietnam might be related to exposure to Agent Orange or to some other chemical during their experience in Southeast Asia. Because serious birth defects occur in approximately 2% to 3% of all live births, the number of such defects that would be expected to have occurred, to date, in children of Vietnam veterans ranges from 50,000 to 150,000. It is not surprising that a veteran who noted a disturbing skin condition apparently associated with his tenure in Vietnam might question whether a birth defect in his child could also be related to that experience.

How might a chemical exposure be related to congenital malformations? Most birth defects result from the abnormalities of development soon after conception, through either teratogenesis or mutagenesis. For teratogenesis to occur, the

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exposure to a putative chemical agent would have to occur in utero. While it is possible that an absorbed and retained chemical from previous exposure might be transmitted to an embryo through semen, it is unlikely. It is possible, however, that a chemical mutagen could produce future birth defects by disturbing the father's germ cells.

It is also possible that exposure to a specific infectious agent encountered while in Vietnam could contribute to an increased rate of birth defects. And while it might not be a *direct* effect of military service, it is conceivable that stress experienced in Vietnam could translate into an unhealthy family milieu with the possibility of inadequate prenatal care, poor nutrition, or abuse of alcohol or other drugs that would adversely affect the pregnancy. Therefore, it is not only important to investigate whether exposure to specific chemical agents could increase the incidence of birth defects, but also whether service in Vietnam alone would have done so.

Donovan and colleagues[6] recently have reported on their experience with birth defects in children born to fathers who had served in the Australian forces in Vietnam. Comparing live-born babies with anomalies diagnosed at, or shortly after, birth with matched infants with no known abnormalities, they could find no evidence that Army service in Vietnam increased the risk of fathering children with anomalies diagnosed at birth. The risk was also independent of length of service in Vietnam or elapsed time from their return to conception of the child. A higher risk in association with longer service might have suggested a dose-response effect, and a decreasing risk over time since return might suggest the excretion of a toxic substance. Because neither of these were demonstrated it may be taken as further evidence for the lack of association.

In this issue of THE JOURNAL, Erickson and colleagues[7] detail their investigation into the possible association between congenital defects and the Vietnam experience of American servicemen. Their conclusions are that Vietnam veterans do not have an increased risk for fathering children with major birth defects, nor do veterans with greater estimated exposures to Agent Orange seem to have an increased risk.

As with all retrospective views of "experiments of nature," the study has some inherent strengths and weaknesses. The authors are meticulous in describing the study's background and careful in qualifying their results.

The data set is derived from a large subset of the Metropolitan Atlanta Congenital Defects Program, a registry of birth defects observed during the first year of life. Attributes of parents of babies with defined defects were compared with those of randomly selected babies born without known defects. The case group and control group were matched to race, year, and hospital of birth. Parents of each group were questioned by interviewers who were blinded as to case or control status in order to eliminate possible bias.

Possible confounding by known contributors to birth defects, eg, maternal age, education, or alcohol consumption, were considered in the lengthy analysis. The investigators were able to evaluate possible birth defect syndromes by considering combinations of two and three defects taken together. They also looked at the effect of malaria or malaria chemoprophylaxis on birth defects.

Because it is impossible to measure accurately the actual herbicide exposure a veteran may have received, the authors have constructed two indices of possible exposure—a veteran's own estimate of possible exposure and an objective scoring system based on the serviceman's location, occupation, and dates of service in Vietnam. While neither one of these two scales relates the possible contribution of ingestion, inhalation, or skin contact of herbicides, they are probably the best estimates of exposure that can be obtained. Although imprecision in exposure might exist, the estimates do not seem to be distorted by any bias. The consequence of this imprecision in the exposure to TCDD is the reduction in sensitivity in detecting specific birth defects.

The authors are appropriately cautious in the interpretation of their results, but considering the overall strength of the study, the past evidence from human exposure, and the confirming experience of Australian servicemen, it would seem that a fairly strong statement can be made that it is unlikely that serious congenital anomalies in children of men serving in Vietnam were results of that experience. That may be of little consolation to those who have suffered the unfortunate circumstances associated with birth defects. But perhaps it will encourage us to expend more effort in preventing birth defects in any child.

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Epidemiologic Notes and Reports

Vietnam Veterans' Risks for Fathering Babies with Birth Defects

Vietnam veterans' risks for fathering babies born with serious structural birth defects were assessed using a case-control study. Case-group babies—those with serious structural defects—were born during 1968 through 1980 and registered by CDC's Metropolitan Atlanta Congenital Defects Program (MACDP). This program registers babies born with structural defects to women who are residents of the five-county metropolitan Atlanta area. To be included in the registry, a baby's defects must have been diagnosed during the first year of life and recorded on a hospital chart by a physician. The use of MACDP as the source of cases precluded analysis of other reproductive outcomes in the fathers or functional deficits, such as mental retardation, in the babies.

Control-group babies—those born without defects—were chosen from among 323,421 babies who were born in the same metropolitan area to resident mothers during the same period. They were frequency-matched to the case-group babies by race, year of birth, and hospital of birth. A total of 7,133 case-group babies and 4,246 control-group babies were eligible for the study. The decision to include fewer control-group babies than case-group babies was based on a review of the anticipated statistical power of the study.

In all, 4,929 mothers of case-group babies and 3,029 mothers of control-group babies completed interviews; fewer fathers completed interviews—3,977 from the case group and 2,426 from the control group. The major reason for parents' not participating in the study was that they could not be located after extensive searching.

Information about paternal military service in Vietnam was obtained during 1982 and 1983 through telephone interviews with the parents of the case- and control-group babies. Vietnam veteran fathers were asked if they believed they had been exposed to herbicides, such as Agent Orange. In addition, a five-level "Exposure Opportunity Index" (EOI) was defined based on activities that may have provided an opportunity for exposure to Agent Orange. Vietnam veteran fathers were given subjective scores by the staff of the Army Agent Orange Task Force reflecting their presumed opportunities for exposure to Agent Orange; the EOI scores were assigned on the basis of times and places of service in Vietnam and occupational duties. Scores were assigned without knowledge of the case/control status of the fathers. Both parents were questioned about a wide variety of other potential risk factors for birth defects. In addition, Vietnam veteran fathers were asked whether they had contracted malaria in Vietnam and whether they had taken malaria chemoprophylaxis there.

Defects occurring among the case-group babies were divided into 96 diagnostic categories for data analysis. Most of the 96 categories were comprised of specific defects, such as anencephaly, ventricular septal defect, and Down syndrome. Some categories were formed by grouping specific types of defects; one comprised all types of defects combined (i.e., the complete case series).

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Birth Defects – Continued

For each of these 96 categories, four hypotheses were tested: (1) whether veterans, excluding Vietnam veterans, were at different risk than nonveterans for fathering babies with birth defects; (2) whether Vietnam veterans were at different risk for fathering babies with birth defects; (3) whether Vietnam veterans who were judged by the Army Agent Orange Task Force to have had greater opportunities for exposure to Agent Orange had different risks for fathering babies with defects; and (4) whether Vietnam veterans who said during the interview that they had been exposed to herbicides, such as Agent Orange, were at different risk. Testing the first hypothesis determined whether, for the tests of the remaining three hypotheses, Vietnam veterans' risks should be compared with those of other veterans or with those of other veterans and nonveterans combined. Testing the second hypothesis was the main focus of this study.

Fathers of 428 case-group babies were Vietnam veterans; fathers of 268 control-group babies were Vietnam veterans. Fathers of 4,387 case-group babies and fathers of 2,699 control-group babies were not Vietnam veterans.

The estimated relative risk of Vietnam veterans' fathering babies with defects when all types of defects are combined was 0.97 (95% confidence limits 0.83-1.14). With few exceptions, the estimated relative risks of Vietnam veterans' fathering babies with defects in the remaining 95 defect groups were similar. Similarly, there was little evidence of different risks for Vietnam veterans who had been assigned higher Agent Orange EOI scores or for Vietnam veterans who had stated during the interview that they believed they had been exposed.

It was determined that, for most defect groups, Vietnam veterans' risks were neither higher nor lower than those of other fathers. In any large study in which multiple statistical tests are done, some exceptions are expected. Some of this study's exceptions are noted below. The estimated risks for fathering babies with spina bifida (imperfectly formed spinal cord) were higher for Vietnam veteran fathers who received higher EOI scores. Vietnam veterans who had higher scores had higher estimated risks for fathering babies with cleft lip with or without cleft palate. Vietnam veterans who received higher scores had higher estimated risks for fathering babies with defects classified as "Other Neoplasms," which include teratomas, neuroblastomas, hamartomas, dermoid cysts, lipomas, central nervous system tumors, Wilms tumor, and miscellaneous benign tumors. Vietnam veterans, in general, had a lower risk for fathering babies with cardiovascular defects classified as "complex" defects (two or more cardiovascular defects). Vietnam veterans who stated they had contracted malaria while in Vietnam had a higher estimated risk for fathering babies born with hypospadias.

No associations between risks of defects and use of malaria chemoprophylaxis were found.

Reported by Chronic Diseases Div, Center for Environmental Health, CDC.

Editorial Note: The most important conclusion to be drawn from this study is that the data collected contain no evidence to indicate that Vietnam veterans have had a greater risk than other men for fathering babies with defects when all types of serious structural birth defects are combined. This study cannot prove that some factor associated with service in Vietnam was or was not associated with the occurrence of rare types of defects, defects in the babies of selected individuals, or defects in the babies of small groups of veterans. The conclusion, however, that Vietnam veterans in general have not fathered, at higher rates than other men, babies with defects when all types of birth defects are combined is based on relatively strong evidence.

All parents are at some risk of having a baby born with birth defects. Because this risk is always there, it is called a "background risk." All men, whether Vietnam veterans or not, who father babies, have the same background risk—about two or three chances out of 100 that their babies will have serious structural birth defects.

Assessing Vietnam veterans' risks associated with exposure to Agent Orange is difficult.

Birth Defects – Continued

The measures of exposure that can be obtained today are imperfect, at best. The ability of Vietnam veterans to give valid reports of exposure is unknown, and the records used for the assignment of EOI scores were made for military purposes, not for health studies. This limitation makes it particularly difficult to assess whether the few statistically significant associations found in this study between defects and greater opportunity for exposure to Agent Orange are likely to reflect true effects of exposure or whether they are merely chance occurrences.

Moreover, the estimated relative risks for the exceptions presented here are rather low. These exceptions could conceivably be due to unmeasured confounding factors and may not be biologically significant. The same reasoning can be applied to the statistically significant association of malaria and hypospadias and the statistically significant association observed for babies with complex cardiovascular defects being fathered by Vietnam veterans.

A summary report of this study has recently been published (*1*), and a more comprehensive report is available from CDC. Copies of these reports can be obtained from CDC's Chronic Diseases Division, Center for Environmental Health.

Reference

1. Erickson JD, Mulinare J, McClain PW, et al. Vietnam veterans' risks for fathering babies with birth defects. JAMA 1984:252;903-12.

TESTIMONY OF MICHAEL GOUGH AND HELLEN GELBAND
OFFICE OF TECHNOLOGY ASSESSMENT
U.S. CONGRESS
BEFORE THE SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
OF THE HOUSE COMMITTEE ON VETERANS' AFFAIRS

REVIEW OF THE CENTERS FOR DISEASE CONTROL STUDY "VIETNAM VETERANS' RISKS FOR FATHERING BABIES WITH BIRTH DEFECTS"

October 3, 1984

Purpose of the Study

The Centers for Disease Control (CDC) undertook this study to find out whether babies fathered by male Vietnam veterans are more likely to have major structural birth defects than are babies fathered by men who did not serve in Vietnam. When planning began for the study, in 1980, there was no method available for assessing exposure to Agent Orange through military records. During the course of planning, however, such a method was developed, and CDC added an "Agent Orange hypothesis" that addressed the question: Is the occurrence of major structural birth defects associated with the father's level of exposure to Agent Orange in Vietnam?

The CDC study was designed and carried out with extensive advice and review by members of the scientific community. Knowledge of that review process and OTA's own reading of the report convince us that the basic design and statistical methods used were appropriate, and that there were no major flaws in data analysis. We fully accept the results of the analyses relating to Vietnam service, but are less certain of the meaning of the results as they relate to Agent Orange. Our reservations stem mainly from uncertainty about the reliability of the Agent Orange exposures indices.

Meaning of the Results

OTA finds that the CDC birth defects study represents, from a practical perspective, the best effort possible toward investigating the potential excess risks of Vietnam veterans fathering babies with birth defects. It also has addressed the question of exposure to Agent Orange and its potential attendant risks for birth defects. The data firmly support the conclusions drawn about the lack of an overall major increase in risk associated with Vietnam service.

The CDC study is the most powerful investigation of birth defects in relation to Vietnam service to date, and probably the most powerful such study possible in the United States. The value of this study, as has been the case with the Air Force's Ranch Hand Morbidity Study (an investigation of the men who participated in the fixed wing aircraft herbicide spray program) and the Australian birth defects study (a case-control study that investigated Vietnam service as a risk factor for fathering a baby with a birth defect) is to set some upper limits on the risks associated with Vietnam service and possibly Agent Orange exposure. The evidence from this study and the Australian birth defects study is consistent, finding no generalized increase in the rate of birth defects associated with Vietnam service.

The Ranch Hand study, which depended on parental recollections and took into account minor birth defects that were not addressed by CDC, found a statistically significant increase in total birth defects in the Ranch Hand group. The Air Force is currently obtaining medical and birth records to fully evaluate questions of birth outcomes in Ranch Handers and a control group. The Ranch Hand study is investigating the effects of Agent Orange, based on the assumption that Ranch Hand personnel were, in fact, exposed. The "Vietnam Experience" is not part of that study, since the comparison group is made up of Vietnam veterans who are similar to Ranch Handers except for their lack of Agent Orange exposure. The Air Force expects to have detailed information about the Ranch Hand birth outcomes in December 1984.

Positive Findings

The positive findings of the CDC study deserve careful scrutiny. First, there were no positive associations of major birth defects of offspring with service in Vietnam, or with self-reported (yes/no) Agent Orange exposure. The three major positive associations -- with "spina bifida," "cleft lip with or without cleft palate," and "other neoplasms" -- were found only with the Agent Orange exposure opportunity indices. Assuming for the moment that the exposure indices are valid, the meaning of positive findings still require interpretation.

The important question is whether those positive associations represent causal associations. The answer to that question involves more than a simple finding of statistical significance. Other aspects to consider include: the magnitude of the excess risk, represented by the "odds ratio;" the biological plausibility of the association; and the consistency of the association with findings from other studies.

Although there are no objective criteria for judging the importance of odds ratios, in general an odds ratio of less than 2.0 is considered relatively small. An odds ratio of 2.0 means that the defect occurs twice as frequently in the case group than in the control group. If a defect usually occurs at a rate of 1 in 1,000, at an odds ratio of 2.0, it would occur at the rate of 2 in 1,000. One of the two could be attributed to the factors at work in the general population, and the one excess case to the factor responsible for the increased risk. The judgement of what is important, of course, must be tempered by the seriousness of the defect and the magnitude of the incidence rate in the general population, or in the population without the risk factor. For something that occurs at a very high rate, a two-fold increase would contribute a large excess, in absolute numbers.

The odds ratios for the categories of birth defects showing increased occurrence in this study all are relatively low, and they occur in categories of fairly low incidence in the general population. The defects, however, particularly spina bifida and other neoplasms, are serious. There is no plausible biological explanation implicating a father's exposure to Agent Orange in producing these defects in children, but we are dealing with an area where few causes are known.

The possibility that the associations are simply due to chance must also be considered, but there is no way to know this based on a single study. The generally accepted level of significance in epidemiology, to which this study adhered, is 0.05, meaning that the probability of the apparent association being due to chance is no more than 5 percent. At this level, if in fact there were no difference, there is still a 5 percent chance of an association appearing. In other words, in 5 out of 100 analyses, one would expect "false positive" results. In this study, with at least two and in most cases three analyses of 96 defects or groups of defects, one would expect some statistically significant findings to occur by chance.

If a study finding represents a true association, the association still may not be causal but can secondary. In a secondary association, both the exposure and the outcome are independently associated with some other, unidentified factor(s). An example is an association of heavy drinking with lung cancer. While drinking does not cause lung cancer, both heavy drinking and lung cancer are associated with cigarette smoking. If one does not take into account smoking habits in studies of lung cancer, an association with drinking would appear. If the true causative factor is unknown, however, it cannot be accounted for in the analysis, and the association will not be explainable by other factors.

A causal association should make biologic sense and should show consistency among studies. In this case, there are no strong biologic hypotheses linking birth defects with a father's previous exposure to Agent Orange. A possible association of Agent Orange exposure and birth defects was worthy of investigation in part because there are few other compelling hypotheses to test.

Participation

OTA has two concerns about the information produced by the CDC birth defects study. First is the low participation rate among "other race" parents. CDC acknowledges this weakness, and places the appropriate caveats around the findings in other race participants. Our concern about this point is lessened somewhat by the fact that there is no known biological reason to suppose that the effect of Vietnam service or Agent Orange exposure would be different among whites and non-whites in the risk of fathering children with birth defects.

Based on the pilot study, CDC predicted that about 70% of eligible case and control parents would participate in the study. The projected 30% who would not participate included both parents who could not be located and those who would choose not to participate. For white case parents, that prediction was reasonably accurate. For the "other race" subgroup, however, participation was much lower. About 60% of other race mothers, and just over 30% of other race fathers completed interviews. The study results, as CDC points out, may be less generalizable to the other race population than are the results for whites to the white population.

Participation by a small percentage of those initially selected raises concern that participants may differ from non-participants. The fact of being difficult to locate in itself may indicate that those people are in some way "different" from those who were located. If those differences are systematically associated with exposures, in this case Vietnam service or exposure to Agent Orange, the results of the study may be influenced. Most of the non-participants in this study were the ones never located. A smaller number declined to take part.

Two types of effects of non-participation are important. First, having fewer cases and controls than planned decreases the power of the study to detect associations even if they exist. The likelihood of "false negative" results is increased. Second, the results might be quite different if the exposure characteristics of the non-participants were known. Unfortunately, the possible biases introduced in this way are unknowable, and the analysis is rightly based on the information that is available.

Agent Orange Exposure Opportunity Indices

Our second and more serious concern is doubt about whether the Agent Orange Exposure Opportunity Indices faithfully reproduce the different exposure histories of veterans. We emphasize that this concern has no bearing on the most significant finding of the CDC study that Vietnam service is not associated with an increased risk of birth defects, but it is key to the interpretation of defects associated with Agent Orange.

Since we prepared our review of the CDC study (sent to Senator Cranston, Senate Veterans' Affairs Committee on September 21, 1984) we have learned more about the assignment of ratings in the the "Agent Orange Exposure Opportunity Indices" that were used in that study. Part of our information was obtained in our role as observers to the Agent

Orange Working Group (AOWG), and that must be held in confidence. However, without compromising confidentiality, we can provide you the basis for our concern that the exposure opportunity indices may not provide an approximation of relative exposure to Agent Orange. In our opinion, the likely misclassification prevents any conclusions based on the Agent Orange Exposure Opportunity Indices.

A method to estimate the likelihood of a veterans' having been exposed to Agent Orange was developed by the Army Agent Orange Task Force. The Task Force outlined their proposed method in a memorandum to the Science Panel of the Orange Working Group (AOWG) in April 1982. In essence, that memo said that the Army could identify the units that a veteran served with in Vietnam. The locations of the units could be determined and plotted on maps against recorded uses of Agent Orange. Men whose units were closer to locations where Agent Orange was known to have been used would be accorded a higher likelihood of having been exposed to the herbicide.

Last week we received, as observers to the AOWG, more details of the Army's methods for assigning a veteran a position in the exposure opportunity index. The methods were presented in a draft to the AOWG, but they are, we understand, essentially what was used in the birth defects study. They provide more detail than the April 1982 memorandum, and they include some subjective judgments of the likelihood of a veteran's being exposed based on the type of unit in which he served.

Inspection of Table 5 of the full report of CDC's Birth Defects Study (copy attached) illuminates our concerns. The table presents examples of military units that were classified on a scale of 1 to 5, with 1 being "minimum opportunities for exposure" and 5 being "most numerous opportunities for exposure." Although the table contains only examples and not a full reporting of classifications, it is noteworthy that "infantry/combat arms" appear only in the high groups 4 and 5 and "noninfantry" appear primarily in groups 2 and 3.

Given men who were in the same proximity to spraying, men in combat units were assigned higher exposure opportunity index scores than were men in non-combat units. With the same objective exposure rating (time and place), a combat soldier and a non-combat soldier could be assigned ratings as much as 3 categories apart, in most cases actually 2 categories apart. In large measure, then, the indices represent service in combat units at least as much as they do exposure to Agent Orange, and because combat plays such an important role in exposure ratings, the true relative Agent Orange exposures may be entirely obscured. If this is the case, and we believe it very possibly is, associations with the indices would have no meaning. What makes this such a vexing problem is that there does not exist, nor is there in prospect, a way to validate any exposure index such as the ones used in this study.

The fact that the two Agent Orange Exposure Indices reported in the CDC study agree with each other reasonably well in their classification of veterans' exposure opportunities is not evidence that they are valid. It only provides assurance of consistency in assigning ratings given the objective information. In one index, military records were used to determine the veteran's units and the locations of the units; in the other index, the veteran's recall was the source of information the units he served with and their locations. In either case, information such as "infantry" or "non-infantry" would almost certainly be the same. If both answers were infantry, the subjective decisions would place the veteran in categories 4 or 5. If the answers were non-infantry, he would be placed in categories 3 or lower. In our opinion, the subjective decisions swamp the other information.

It may be that combat units were more exposed, given identical objective exposure information, but the arguments are far from convincing. We think that there is probably no way to develop a reliable exposure index, and we do not attribute this situation to failure on the part of any individuals or institutions. The best people have tried, with the best information they could develop, without a satisfactory outcome.

The validity or lack of validity of the Agent Orange Exposure Opportunity Indices does not in any way affect the conclusions about associations of birth defects with Vietnam service. If the indices are invalid, however, the Agent Orange analyses provide no reliable information either to rule out associations with Agent Orange or to confirm them.

Table 5. Examples of Agent Orange Exposure Opportunity Index Scores[a]

Index Score = 1 (minimum opportunities for exposures)

1. Service in selected locations at specific times
   (any job description except handling Agent Orange)
   - e.g., Cam Ranh Bay (66)
     Qui Nhon (68-69)
     Nha Trang (67-68)
2. Non-Ranch Hand pilots and aircrew (66-67)
3. Specified Controlled Environments
   - e.g., battalion surgeon (68)

Index Score = 2

1. Service in selected locations at specific times
   - e.g., Gia Le (69-70)
     Phan Rang (other than 9-12/68,3-9/70)
     Qui Nhon (68-69)
2. Selected noninfantry occupations at specified places and times
   - e.g., company clerk — Duc Pho (68-69)
     radio repairman — Chu Lai (66-67)
     truck driver — Cu Lam Nam (68)
3. Noninfantry stationed at selected bases with perimeter spraying
   - e.g., wireman — Chu Lai (68-69)

Index Score = 3

1. Service at bases with perimeter spray operations, specified times
   - e.g., Chu Lai (68-69) — Camp Eagle (68-69)
     LZ English (67-68)
2. Selected noninfantry occupations at specified locations and times
   - e.g., salvage specialist — Danang (69-70)
     M.P. — Danang (68-69)
     wheeled vehicle mechanic — Long Binh (66-67)

Index Score = 4

1. Infantry/combat arms at specified locations and times
   - e.g., An Khe (66-67)
     Tam Ky (67-68)
     Tay Minn (69-70)
2. Selected noninfantry at specified locations and times
   - e.g., Helicopter pilot — Cu Chi (66-67)
     M.P. — Long Binh (67-68)
3. Advisors of Army, Republic of Vietnam Divisions (68-69)
4. Special Forces Camps (field personnel)
   - e.g., Nha Trang (69-70)

Index Score = 5 (most numerous opportunities for exposure)

1. Infantry/combat arms at specified locations and times
   - e.g., A Shau Valley (69)
     Tay Ninh (68)
     Phuoc Vinn (67)
2. Service at specified locations and times with aborted Ranch Hand missions or other herbicide mishaps
   - e.g., Bien Hoa AFB (7/67, 11/68)
     Long Binh Post (67-69)
     Phu Cat AFB (69-70)

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[a] See text for description.

CHARTER
(As Amended May 1984)

Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants

Purpose

By memorandum of December 11, 1979, the Assistant to the President for Domestic Affairs and Policy directed the establishment of an Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants (Work Group) under the leadership of the Secretary of Health and Human Services. The Work Group was specifically directed to assure that the protocols and methodology of proposed federal research studies will provide reliable data, as well as to provide technical support to individual agencies in the implementation of research.

On August 1, 1980, the Work Group recommended that the United States Air Force conduct its proposed Epidemiologic Studies of Ranch Hand Personnel (Rand Hand Study) and that the conduct of the study be overseen by an independent monitoring committee. By memorandum of September 16, 1980, the Assistant to the President for Domestic Affairs and Policy directed the Air Force to conduct the Ranch Hand Study. In addition, the memorandum directed the Scientific Panel of the Work Group, augmented by scientists from outside the government and including those suggested by veterans organizations, to oversee the study and to provide technical assistance, as needed, to the Air Force.

On July 17, 1981, the President re-established the Interagency Work Group as the Agent Orange Working Group (AOWG) and elevated it to Cabinet Council status. On August 21, 1981, the Secretary, DHHS, Acting as Chairman Pro-Tem, Cabinet Counsel on Human Resources, reaffirmed the Work Group's mandate of December 11, 1979 and appointed the Deputy Undersecretary for Intergovernmental Affairs as Chair of the AOWG.

Authority

The Committee on Special Studies was established under the provisions of section 222 of the Public Health Service Act, as amended, 42 U.S.C. 217a. The Committee is governed by the provisions of 45 CFR Part 11 which sets forth standards for the creation and use of advisory committees.

Function

The Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants shall advise the Secretary and the Chair, Cabinet Council Agent Orange Working Group (AOWG), concerning:

1. Its oversight of the conduct of the Ranch Hand Study by the Air Force;
2. It oversight and evaluation of the Agent Orange/Vietnam Experience Study mandated by Section 307 of P.L. 96-151 as amended by P.L. 97-72; and
3. Other studies in which the Secretary or the Chair, AOWG, believes involvement by the Advisory Committee is desirable.

The Advisory Committee may provide technical assistance to the study under its consideration.

On the basis of its oversight and evaluation, the Advisory Committee may, *inter alia*, recommend to the Secretary and the Chair, AOWG, (a) approval, (b) deferral because of a need for further evaluation, (c) disapproval in whole or in part, or (d) imposition of additional conditions which in its judgemnt are necessary to assure or protect advancement of the study under consideration.

Structure

The Committee shall consist of the Secretary, or designee, as Chair, and eight members selected by the Secretary from authorities knowledgeable in fields related to the studies under its oversight and evaluation. The Executive Secretary shall be selected by the Chair.

Management and support services shall be provided by the National Cancer Institute.

Meetings

Meetings shall usually be held quarterly at the call of the Chair, who shall also approve the agenda. A government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of the proceedings kept, as required by applicable laws and Departmental regulations.

Compensation

Members who are not full-time federal employees shall be paid at the rate of $100 per day, plus per diem and travel expenses in accordance with Standard Governmental Travel Regulations.

Annual Cost Estimate

Estimated annual cost for operating the Committee, including compensation and travel expenses for members but excluding staff support, is $19,736. Estimate of annual man years of staff support required is one-quarter, at an estimated annual cost of $8,380.

Reports

An annual report shall be submitted to the Secretary through the Assistant Secretary for Health not later than November 1 of each year, which shall contain as a minimum a list of members and their business addresses, the Committee's functions, dates and places of meetings, and a summary of Committee activities and recommendations made during the fiscal year. A copy of the report shall be provided to the Department Committee Management Office.

Termination Date

The duration of the Advisory Committee on Special Studies Relating to the Possible Long-Term Effects of Phenoxy Herbicides and Contaminants is five years. Unless renewed by appropriate action prior to its expiration, the Committee will terminate on January 19, 1985.

Agent Orange Working Group Mandate
December 11, 1979, as reaffirmed on
August 21, 1981

The Agent Orange Working Group shall:

1. Oversee, coordinate, and set priorities among Federal government research activities designed to relate exposure to phenoxy herbicides to long-term health effects.

2. Design a research agenda to assure that the Federal government conducts comprehensive research on the long-term health effects of these compounds, in response to both scientific and policy needs. The type and duration of exposure to Agent Orange by Vietnam veterans must be considered in the research agenda design so that the Veterans Administration will be able to establish sound policies for determining compensation for veterans exposed to Agent Orange in Vietnam, should a relationship between herbicide exposure and long-term adverse health effects be established. The research agenda should build on current agency activities, including the Department of Defense's Ranch Hand study. The interagency work group should identify the appropriate agencies to conduct the recommended research, either individually or through joint efforts.

3. Provide technical support to individual agencies and independent researchers in the formulation, development, and implementation of research on the biomedical effects of phenoxy herbicides and contaminants.

4. Assure that the protocols and methodology of ongoing and proposed federally funded research studies will produce valid, reliable, timely, and relevant data, and periodically review the status of such research.

5. Assure that all relevant research findings, whether publicly or privately financed, are promptly made available to the public and the Congress, in a comprehensive fashion. The work group should establish a working relationship with the Veterans Administration's Advisory Committee on Health-Related Effects of Herbicides and should promptly provide the Committee all relevant information as it becomes available.

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